About this book

This book is an expanded and updated version of the earlier A Lay Person's Guide to Medicine published in December 2000.

This book is a renewed attempt to alert the reader to the widespread crisis in medicine created by drug policies which go against the safe interests of all people. India's pharma industry and stock markets are "shining" and booming, but by and large it is a story of poverty and inadequacy amidst plenty.

Medicines and the pharma industry have started to occupy center stage in the public imagination thanks to the vigorous contestation on patents, intellectual property rights, WTO, HIV/AIDS drugs at low prices, and so on. From January 2005, India abandoned a process patent regime that served it well. India is in the process of opening up its health sector for the dollars it brings, even as India's pharma elite is rapidly trying to "integrate" with the global ruling class.

LOCOST (Low Cost Standard Therapeutics), founded in 1983, is a not-for-profit trust based at Vadodara (Baroda), India. LOCOST is committed to the promotion of rational therapy and people-oriented drug and health policies. It makes available good quality, essential medicines at low prices.

A Lay Person's Guide to Medicines

LOCOST

The Revised

A Lay Person's Guide to Medicines

What is in them and what is behind them

LOCOST, Vadodara, 2006

About this book

This book is an expanded and updated version of the earlier *A Lay Person's Guide to Medicine* published in December 2000.

This book is a renewed attempt to alert the reader to the widespread crisis in medicine created by drug policies which go against the safe interests of all people. India's pharma industry and stock markets are "shining" and booming, but by and large it is a story of poverty and inadequacy amidst plenty.

Medicines and the pharma industry have started to occupy center stage in the public imagination thanks to the vigorous contestation on patents, intellectual property rights, WTO, HIV/AIDS drugs at low prices, and so on. From January 2005, India abandoned a process patent regime that served it well. India is in the process of opening up its health sector for the dollars it brings, even as India's pharma elite is rapidly trying to "integrate" with the global ruling class.

LOCOST (Low Cost Standard Therapeutics), founded in 1983, is a not-for-profit trust based at Vadodara (Baroda), India. LOCOST is committed to the

A Lay Person's Guide to Medicines

LOCOST

A Lay Person's Guide to Medicines

What is in them and what is behind them

LOCOST, Vadodara, 2006

A Lay Person's Guide to Medicines

What is in them and what is behind them

-

Low Cost Standard Therapeutics (LOCOST)
Vadodara, India
2006

This book is in the spirit of Copyleft.
Anybody can copy this work for public purposes provided the works derived there from could also be reproduced free of cost for public interest and for non-commercial purposes only. Acknowledge us in works if you have reproduced from this book.

Revised, enlarged edition (2006) of the original 2000 book.
Published by
Low Cost Standard Therapeutics (LOCOST)
1st Floor, Premananda Sahitya Bhavan, Dandia Bazar
Baroda 390 001, Gujarat, India
Ph: 91 265 2413319 (office); 2830009/2831468 (factory)
Fax: 91 265 2830693, 2830999
E-mail: locost@satyam.net.in
Web : www. locostindia.com

Suggested contribution: Rs. 300/-, US $ 15/-

Back Cover Cartoon: Nilabhodhar Chowdhury
Typeset at Graphic Communication, Vadodara
Printed at Hinglaj Printers, Ahmedabad, India

ABOUT THIS BOOK

Much water has flown in since we last published the well-received, earlier version, *A Lay Person's Guide to Medicine*, in 2000.

Medicines[1] and the pharma industry have started to occupy center stage in the public imagination thanks to the vigorous contestation on patents, intellectual property rights, WTO, HIV/AIDS drugs at low prices, and so on. In a way this is good to have it out in the open. Health and pharma have always been politics than merely science, and it is in the interest of us all that the politics of medicine, and indeed the economics of it, are coming out, warts and all.

From January 2005, India abandoned a process patent regime that served it well. We have thrown open even our health services in the perverted logic of health tourism dollars. India's pharma elite is rapidly trying to "integrate" with the global ruling class and elites. As a fallout, the Government of India tends to accede to things in international arena that are not always in the larger national interest, and especially not in the interest of those for whom life is still a hand-to-mouth struggle.

This book is a renewed attempt to share with concerned citizens, the distortions that have crept in the pharma sector of India, and globally too, and what we can do about them. This book continues to be informed by concerns that access to health is part of the fundamental human right to life. Therefore, health of the people needs to take precedence over all other policy actions of the government, and related maneuvering of the drug industry and associated lobbies. In our search to make the drug industry world class, our policy makers tend to forget that the pharma industry has to subserve human goals of becoming and being healthy, and that industry cannot operate in some isolated heady goal of world class that may at best help the business elite of India to dominate world markets.

Likewise, drug regulatory agencies are not here, or should not be, to facilitate drug companies but to facilitate the industry to help people access quality drugs and affordable health care. It will be in the interests of all citizens if the decisions of various committees like the Drug Technical Advisory Board, and of the Drug Controller of India, are out in the public domain in a publicly accessible website. And also information about who is doing what clinical trials in India is a necessary precondition for our collective safety.

WhysomuchInformation?

Most doctors tend to ask why lay persons should know "so much" information as especially given in the latter part of the book. Would *they* understand, would it not prevent quackery, overmedication, etc? We say in response that it is the duty of those privileged, by accidents of birth and/or otherwise, to demystify their actions especially those having a bearing on the life and death issues of the general public. Do we need to understand nuclear physics in all its mathematical regalia for us to know nuclear bombs are a no-brainer and that nuclear power is an economic *cul de sac*?

Indeed the "lay" public needs to know the broad contours of many so-called technical issues: medicine and science, like politics and economics, are too important to be left to their primary practitioners. As the many instances cited in this book show, the nexus between drug industry, medical profession, regulatory agencies and policy makers has given little cause for comfort for the majority of us.

[1]Throughout this book we use the terms "drugs" and "medicines" interchangeably to mean pharmaceuticals for human therapeutic use that are not narcotics.

This book would not have been possible but for the existence in India of a group of women and men of the medical profession who have stayed true to the ideals of their profession as exemplified by the Hippocratic oath and the ideals enumerated in the *charaka samhita*. These friends are, among others, members of such networks as the Medico Friend Circle, the All-India Drug Action Network, the Jan Swasthya Abhiyan and the Forum for Medical Ethics to name a few. Indeed, we have a number of doctors and technical experts willing to take time to demystify the issues involved; and join protest rallies if need be. In Bangladesh, the roll of honor is headed by the indefatigable Dr.Zafrullah Chowdhury, the main architect of the Bangladesh Drug Policy who continues to be a source of inspiration for many in India and elsewhere.

But not all of us, in this one billion plus country, have access to such doctors. The majority of us, who are not doctors, have little or no access to information about the use and effects of medicines. Our experience tends to be that most doctors have very little time and/or inclination to inform their clients about the correct use of the medicines they prescribe. This book is an effort to fill the gap.

However, this book is not a substitute for a good doctor. Or a standard textbook of pharmacology. But in the absence of access to authentic information from a human, personalised source which is the case with most parts of India, urban and rural, this book is an important low-priced resource.

Social action groups without access to qualified medical practitioners often have innovated by training non-medical persons in a few relevant and essential medical skills: the village health workers and the "barefoot" dai for instance. This book will be of use to such groups and persons. It will also be of help to a whole range of literate, non-medical persons who want to use medicines in a more informed way.

More importantly, we aim to alert the reader to the widespread crisis in medicine created by drug policies which go against the safe interests of all people. India's pharma industry and stock markets are "shining" and booming, but by and large it is a story of poverty and inadequacy amidst plenty.

Obviously, we need more such books in all languages of India. A Hindi version would be also available shortly. We welcome translations and adaptations. Please do inform us before you do so.

On behalf of LOCOST, the undersigned thanks the many individuals and groups who have contributed to this book and otherwise encouraged us.

July 2006

S. Srinivasan

Vadodara, Gujarat, India.

Managing Trustee, LOCOST

FOREWORD TO EARLIER VERSION[1]

Medical information is exploding and along with it, the internet revolution. A lot more information is now easily available. But still internet is inaccessible to most people in the third world. The explosion of medical information seldom caters to ordinary literate lay persons.

A Lay Person's Guide to Medicine by LOCOST attempts to fill the gap. This book is a necessary addition to the vast and burgeoning literature on the do's and don'ts of medicines. The contributors have gone to great trouble to sift the vast information available and put relevant information of immediate use to consumers.

This genre of books so long had remained sighted in the western market and usually is written or compiled by western authors. *A Lay Person's Guide to Medicine* from LOCOST is a courageous attempt. Books targeted towards consumer's education usually omit the discussion on the politics of the drug industry, the unfortunate nexus between the medical profession and the pharmaceutical industry, and the lackadaisical response of policy makers. Governments seldom see drug industry as a health issue and are only too eager to please the industry.

The effects of the WTO on the drug industry has a place in the book. One has to necessarily examine the impact of product patents on India's drug industry - a matter of deep concern to all observers in developing countries. These happenings are deeply violative of fundamental human aspirations to equality and right to life.

LOCOST has been consistently, and if I may add ethically, promoting the idea of rational essential drugs by actually making them available and at low prices. This book will be another tool for people's groups to educate themselves in their struggle for equitable health. Last, but not the least, it is important to mention that the LOCOST team, having well-qualified professionals, has always worked as an enlightened development and health activist group true to the causes of the poor, who are continually becoming further improverished due to wrong health care policies and costly, inappropriate medicines.

Congratulations to LOCOST for enlightening health workers, including physicians, and lay people.

Wider distribution of *A Lay Person's Guide to Medicine* will surely help reducing some exploitation of the common people.

I again congratulate LOCOST on bringing this book and urge them to immediately bring out language versions in the many languages of India.

Dr. Zafrullah Chowdhury
Gonoshasthaya Kendra, Dhaka, Bangladesh

November 12, 2000

[1] *A Lay Person's Guide to Medicine: What is behind them and how to use them.* LOCOST, Baroda, 2000.

PREFACE TO EARLIER VERSION

This book aims at providing necessary information about prescription drugs to the population at large. When a doctor prescribes a drug, he/she is expected to tell the patient some important points. These points should include not only the dose but also precautions to be taken in case of any adverse effects. In practice this does not happen since doctors are busy and have no spare time for such activities.

The book tries to bridge this gap so that the use of these drugs will have some information regarding proper utilisation of the prescribed drugs. Information on commonly prescribed drugs - in the form of generic names, usage and dosage of drugs, common side-effects, and adverse and toxic effects - are listed in the book. The latter have been classified into two groups: users who can continue the drug but just need to inform the doctor regarding the adverse effect; and those who need to stop the drug so that further damage can be halted. Dosage information given in the book will be useful to the patient as doses mentioned in the book are the usual dosages used in clinical practice. However, sometimes the practising doctor may increase or decrease the dose.

In pregnancy, many, if not most, drugs are to be avoided. Only those drugs which are prescribed by a doctor need be taken. Drugs prescribed for another patient, though apparently for the same condition, should not be, normally, used. In case of any allergic reactions and/or abnormal symptoms after starting a drug, the doctor needs to be informed about the same. Adverse conditions under which the doctor definitely needs to be consulted are specified in the book to an extent possible.

Dr. P. S. Patki
Professor of Pharmacology
B. J. Medical College, Pune 411 001, India

ACKNOWLEDGMENTS

This book has seen considerable chopping and additions from the earlier version, *A Lay Person's Guide to Medicine* (Baroda, 2000). We are grateful to a number of persons who have given feedback, positive and for the betterment, on the 2000 version of this book. We have added a couple of chapters on relevant issues that have surfaced in recent years: patents, pricing, clinical trials and conflicts of interest and a chapter on Women and Medicines. We have added a lot many profiles of drug classes in Chapter 1 and they are all the painstaking work of Dr. Ravi D'Souza. The chapters on rationality and pricing of drugs have benefited by the work and attention of Dr Anurag Bhargava of Jan Swasthya Sahayog (JSS), Bilaspur. A great many data have been taken from the LOCOST/JSS publication, *Impoverishing the Poor: Pharmaceuticals and Drug Pricing in India* (Baroda/Bilaspur, Dec 2004). The works, and insight, of Dr.C.M.Gulhati, Editor, *MIMS India* have been quoted/used freely. Other friends who have given valuable feedback and more importantly constant encouragement are: Dr. Zafrullah Chowdhury, who was kind enough to write the Foreword to the earlier version, Dr. Anant Phadke, Dr. Mira Shiva, Dr. Wishvas Rane, Dr. Sunil Kaul, Dr. P.K. Sarkar, who edits *BODHI* (*Bulletin of Drug and Health Information*), and Dr.Gopal Dabade. You will find them all cited at several places in the text. Others whose works have been reproduced with kind permission are that of Dr. N.K.Gurbani and Dr. R.R.Chowdhury. The chapter on Patents has greatly benefited from the writings of Shri Keayla, the discussions at the IP Health e-forum and by the writings of James Love of Consumer Protection for Technology (CPTech), and by the work of the Medicine Sans Frontiers (MSF). T.Srikrishna of LOCOST has contributed to the chapter on pricing. The SAMA Delhi team went through the chapter on Women and Medicines. Page design of the book is due to S.M. Graphics, Vadodara. Cover design and illustrations were improved upon by C.Kokje who also did the actual page layout and organisation.

We have also copied/reproduced, from the *BMJ* especially, in public interest. Many others have been copied in the spirit of Richard Stallman of free software and Copyleft movement whose gnu symbol we have reproduced on the credits page. We thank CENTAD, New Delhi for permission to reproduce cartoons from *Trading Up.*Those we have failed to acknowledge/cite, please forgive us our oversight. Many of the websites quoted were accessed between June 2005 to June 2006 and some even earlier. In case they do not open, please do a google search for the new web location in case they have moved.

We are grateful to the following persons for their contributions to the earlier version of this book (acknowledgments as for the 2000 edition in so far relevant for the current edition.).

Overall vetting of technical contents of drug information:

Dr. P. S. Patki, M.D., Prof. of Pharmacology, B. J. Medical College, Pune; Dr. Medha Kshirsagar, M.D., and Dr. Deepak Langade, MBBS, of the Dept. of Pharmacology, B. J. Medical College, Pune; and Dr. Anant Phadke, Medico-Friends Circle, Pune. Feedback on 50 Drug Profiles, Section 2: Dr. K. C. Dave, Prof. of Pharmacology, Ahmedabad (since deceased); Dr. P. K. Sarkar, Prof. of Pharmacology and Editor, BODHI, Calcutta; Dr. W. V. Rane, Pune; Dr. Gopal Dabade, Dharwar; Dr. Ravi D'Souza, Bhubaneshwar; Dr. S. Sridhar, ARCH-Mangrol; Dr. Kiran Shinglot, Baroda; Dr. Anant Phadke, Pune; Dr. Ulhas Jajoo, Prof. of Medicine, Sewagram; Dr. Bipa Mazmudar, Asst. Prof. of Pharmacology, Baroda; and Dr. Rajesh Mehta, Asst. Prof. of Community Medicine, Ahmedabad. We thank the Indian Academy of Paediatrics (IAP) for kind permission to use their posters on Rational Drug Therapy as well as questions and answers from their book Rational Therapy in Paediatric Practice used in Section 3 of this book.

Overall Planning and Editing: S. Srinivasan, Vaishali Patel, Lakshmi Menon and T. Srikrishna. Chapter 1: Vaishali Patel; Chapter 2-4: Lakshmi Menon, Dr. M. Bagchi and S.Srinivasan; Chapter 5: Lakshmi Menon and Vaishali Patel; Chapter 3, Appendix 1: Dr. Sagun Desai, M.D., Prof. and Head, Dept of Pharmacology, P S Medical College, Karamsad, Dt. Anand, Gujarat; Sections on Insulin, Steroids, ORS, Oral Contraceptive Pills and Vitamin A: Dr. Ravi D'Souza

Section 2, Profiles of 50 Drugs: Vaishali Patel and Dr. Madhuchhanda Bagchi
Section 3, Short Profiles of 107 Drugs: Rita S. Desai and Yamini Purohit, doctoral scholars in Biochemistry
In addition T. Srikrishna contributed enormously in editing the drug profiles for consistency and filling in information gaps.

We have also borrowed freely illustrations from other publications. We have tried to get permissions wherever we could. We thank them all.

Data Entry: V. Balakrishnan, T. Laxmi Saraswati; and Sharad Panchamiya of Page Setter.
Needless to add, LOCOST alone is responsible for any errors that may have crept in.

HOW TO USE THIS BOOK

This book is a guide for consumers on the use of pharmaceutical drugs, otherwise known as allopathic/modern medicines. And for those interested in the political economy of the pharmaceutical industry. It is divided into four sections.

Section 1 contains five chapters. Chapter 1 discusses what are drugs and gives details of drug classification, forms of drugs and administration, drug action and effects, drug dependence, drug storage and poisoning. It guides us in discussing the management of our drug treatment with our doctors and suggests precautions to be taken while on drug therapy. This chapter tells how to evaluate the drug profiles given in Section 2.

The second chapter on Essential Drugs explains the World Health Organization (WHO) concept of essential medicines which primarily aims at eliminating irrational drug therapy and promotes safe and efficient use of medicines at low cost. It also discusses the necessity for promoting medicines by their generic names rather than brand names. The next chapter on Rationality of Drugs describes the criteria for rational drug therapy. It gives information on combination drugs, and explains the irrationality of some combination drugs and gives a list of combination drugs which are hazardous. To understand the marketing practices of pharmaceutical companies, Chapter 4 briefly discusses the drug industry in India, and their unethical practices in drug promotion and pricing. The chapter includes a discussion on the misuse of medicines and a critique on various guidelines for ethical marketing. Chapter 5 continues the discussion with the focus on doctors, drug industry and clinical trials. Chapters 6, 7 and 8 respectively deal with patents, pricing of formulations, and the interfacing of women and pharmaceuticals. The last chapter, Chapter 9, in this section deals with policy changes and action needed by consumers. As becomes apparent from the preceding chapters, consumers need to be alert and cannot put their trust entirely on doctors or expect pharmaceutical companies to provide unbiased information on the medicines they market. It lists different ways consumers can initiate action.

Information given in Sections 2 and 3, may, hopefully, help us know more about the drug we are consuming and how about how they work. This knowledge may give a better understanding of our bodies which can help us exercise an informed choice in treatment. Indeed, it may even be possible that a particular drug may not be necessary at all. And this knowledge will help us discuss our health problem and its solution with our doctors.

Section 2 contains detailed profiles on 50 of the more commonly used medicines while Section 3 presents briefer information on some 100 other commonly used medicines.

Section 4 includes a glossary of technical terms and a guide to some essential reference material.

CONTENTS

About this book 3
Foreword to earlier version 5
Preface to earlier version 6
Acknowledgments 6
How to use this book 8
Index of Drug Profiles 11

Section

Chapter 1: About Drugs in General **15**

1. Drug Forms and Administration *6*
2. Evaluation of Drug Profiles *19*

Annexure 1 Some Common Drug Categories and How they Work 47
Annexure 2 Poisoning and its Treatment 87

Chapter 2: Essential Drugs **92**

1. Why We Need Only Essential Drugs? *93*
2. Why an Essential Medicines List? *96*
3. Generic/Brand Names, Innovator Products and Generics *101*
4. Implementation of Essential Drugs Idea in Two States of India *112*

Annexure 1 Criteria for Withdrawal of Irrational and Hazardous Drugs: the Bangladesh Example 115
Annexure 2 Access to Medicines: How India Stands Globally? 117
Annexure 3 Country Specific Approaches to Updating Essential Drugs and Formulary Lists 119
Annexure 4 Right Brands; Wrong Medicines Dietary Salt Dispensed in Place of Epilepsy Drug 120

Chapter 3: Rationality of Drugs **122**

1. What is Rational Therapy? *123*
2. Causes of Irrationality *129*
3. Combination Drugs: When Drug Combinations are Rational *139*
4. Vitamins and Tonics
5. Hazardous Drugs *143*

Annexure 1 Why Some Leading Drugs in the Indian Market should not be sold - but are still sold 154
Annexure 2 Dubious FDCs Being Marketed in India … not Approved by DCGI and hence Illegal 160
Annexure 3 List of Drugs Prohibited for Manufacture and Sale through Gazette Notifications 162
Annexure 4 Identification of Harmful, Irrational and Useless Analgesics 165
Annexure 5 Irrational Combinations of Paracetamol 167
Annexure 6 Rofecoxib, Heart Attacks and the FDA: Testimony of David J. Graham 169

Chapter 4: Marketing of Drugs **178**

1. Pharma Scenario in India *178*
2. Marketing of Top 300 Drugs in India: A Brief Analysis *181*
3. Marketing of Drugs and the Abandoning of Quality and Ethics *188*
4. Manipulating Quality *192*

5. Prevalence of Spurious Drugs *194*

Annexure 1 Landmark Incidents in the Unethical Marketing of Drugs 201

Chapter 5: Drug Promotion, Clinical Trials and Conflicts of Interest **208**

1. "Forms of Entanglement" *208*
2. Clinical Trials, Research Publications and Conflicts of Interest *217*
3. Conflicts of Interest and Codes of Marketing *231*

Annexure 1 What are Clinical Trials? 235
Annexure 2 Conflict of Interest: My Journey 239
Annexure 3 WHO Ethical Criteria and IFPMA Code of Pharmaceutical Marketing Practices 241

Chapter 6: Patents, Trade and Availability of Medicines **247**

1. Free Trade, WTO/TRIPS and the Pharma Industry *248*
2. India, Patents and TRIPS *258*
3. Possible Impacts *271*
4. What is to be done? *279*

Annexure 1 TRIPS in WTO: Is it Logical? 284
Annexure 2 Openness Promotes Growth? 285
Annexure 3 For Free Trade in Ideas 285
Annexure 4 Unfairness of Free Trade: WTO, a Neutral Arbiter? 287
Annexure 5 Some of the Useful Recommendations in the CIPIH Report 290

Chapter 7: Pricing and Availability of Drugs **299**

1. Need for Price Control *299*
2. Health and Political Context of Price Control *311*
3. Some Positive Initiatives and Reports *318*
4. How much do Drug Formulations Actually Cost and can Cost *324*

Annexure 1 Pricing and Price Control of Drugs and Pharmaceuticals 326

Chapter 8: Women and Medicines **333**

1. Medicines and Women's Health *333*
2. Misuse of Drugs and its Effects on Women *337*
3. Contraceptive Drugs and Women *341*
4. Hormonal Replacement Therapy (HRT) *347*
5. Other Concerns *348*

Chapter 9: What is to be done? **356**

Section Profiles of 50 Drugs **363**
Section Short Profiles of 107 Drugs **505**
Section **583**
Primary and Secondary Information Sources on Drugs & Related Health Issues 583
Glossary 593 About LOCOST 597 About All-India Drug Action Network 598

Section

Chapter 1
About Drugs in General

Drugs are chemical substances which affect living organisms. Such substances, also known as medicines, are used to detect, cure and prevent diseases, and relieve symptoms. Many drugs are synthetic forms of naturally occurring substances, that is, chemical copies of the original. Some are obtained from botanical or animal sources, for example, belladonna used for some gastrointestinal problems is derived from the deadly night shade; opiate drugs including morphine are derived from certain types of poppy. Many vaccines, thyroid hormones and insulin (until recently) are obtained from animal sources. Some hormones are produced in the laboratories. The process involves altering certain micro-organisms at the genetic level and thereby changing the products of cell activity. For instance, the hormone insulin which is produced naturally by humans can now be manufactured by genetically-engineered bacteria. Most drugs are produced by pharmaceutical companies through chemical processes. They are marketed only after testing for safety and efficacy. Testing is done on animals and human volunteers. Drugs cannot be marketed without the approval of the Food and Drug Administration (FDA), also called the Drug Controller/Commissioner in some states. The highest drug control authority in India is the Drug Controller General of India (DCGI).

1. Drug Forms and Administration

According to the Drugs and Cosmetics Act 1940 of the Government of India, the term "drug" includes:

> (i) All medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes;
>
> (ii) Such substances (other than food) intended to affect the structure or any function of the human body or intended to be used for the destruction of [vermin] or insects which cause disease in human beings or animals, as may be specified from time to time by the Central Government by notification in the Official Gazette;
>
> (iii) All substances intended for use as components of a drug including empty gelatin capsules; and
>
> (iv) Such devices intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, as may be specified from time to time by the Central Government by notification in the Official Gazette, after consultation with the Board.

Please note that even certain devices are called drugs under this definition, which implies that a CAT scan

machine, or an ultrasound machine, or a stent (see box below) would be a drug. We use the term "drugs", or "medicines", in this book mostly in the sense of (i) above.

Drugs are available to be administered (that is, dispensed) in the human body in various forms: as tablets, capsules, liquids (for example syrups, drops), injection solutions, topical creams (ointments), suppositories and pessaries, eye and ear drops, nasal drops and sprays and inhalers. These forms are specially designed for the needs of administration and to ensure correct dosage. Sometimes colouring and flavouring and other inactive ingredients are added to the drug. These ingredients are added to improve the chemical stability and to extend efficacy of the drug for a longer period of time.

Let us look at some of the available forms (or "presentations") of drugs (see also the box below on efficacy of various dosage forms).

Tablet: The drug is compressed in a solid form, mostly round in shape. Other ingredients are added to it like diluents (sucrose, lactose, sodium chloride), binders (acacia, gelatin, glucose), granulating agents (gum, water, starch pastes), lubricants (magnesium stearate, purified talc) or disintegrating agents (starch, sodium bicarbonate, tartaric acid). **Tablets are the cheapest form of a given medicine.**

Capsule: A capsule is a gelatin shell in cylindrical shape containing the drug. The shell breaks open when swallowed. Slow-release capsules contain pellets which dissolve in the gastrointestinal tract. Slow-release or controlled release capsules/tablets are dosage forms that release medication over extended time periods to avoid high concentrations in the digestive tract or to provide longer duration of action than are available through conventional dosage forms. Some abbreviations used normally here are: LA (Long Acting); SA (Sustained Action); SR (Sustained Release); TR (Time Release); ER (Extended Release).

Liquids: Many drugs in liquid form may have its active ingredients combined in a solution, suspension or emulsion with other inactive substances such as solvents, preservatives, flavouring and colouring agents. Different forms of liquids include mixture, elixir, emulsion or syrup:

- a mixture contains one or more drugs either dissolved to form a solution or suspended in a liquid.
- an elixir is a solution of drug in sweetened mixture of alcohol and water and is often flavoured.
- an emulsion is a drug dispersed in oil and water. An emulsifying agent is included to stabilise the product,
- a syrup is a concentrated solution of sugar containing the active drug with flavouring, colouring and stabilising agent (s).

Tablets, capsules and liquids are administered to the patient by mouth.

Topical skin preparations are only for external use. They are applied on the skin. They include:

- cream which is non-greasy and is used to apply drugs to the skin, to cool or moisten the skin.
- ointment which is greasy preparation used to apply drugs or act as protective or lubricant layer for the relief of dry skin conditions.
- lotion which is a solution or suspension applied to unbroken skin.

Quality Control on Condoms but not Coronary Stents

Believe it or not: till October 6 this year (2005), while there were stringent rules to regulate the quality, import, manufacture, distribution and sale of condoms but absolutely no check on cardiac stents! Every Tom, Dick and Harry was at liberty to import or locally manufacture any medical device, including drug coated coronary stents, cardiac valves, catheters, intraocular lenses, prostheses used in total knee replacement and other similar intrusive, indwelling items without any clearance or quality control from any one. No wonder medical devices, not even approved for use in their countries of origin, such as Axxion Drug Eluting Stents from Holland, were finding their way to free-for-all Indian market and being sold at fancy prices to ill-informed patients often in connivance with doctors.

Alarmed at such lawlessness, the Bombay High Court ordered the Drugs Controller General, India (DCGI) to bring all such sensitive, sterile, life-saving items within the purview of Drugs and Cosmetics Rules. In compliance, the Ministry of Health was left with no alternative but to issue two Gazette notifications on October 6 and 7: firstly, to declare that such medical devices will be deemed to be "drugs" and secondly, they will need DCGI licence.

Why did it become imperative for a court of law to intervene? The answer lies in the English proverb: you can take a horse to water but you cannot make it drink. For the past half a century, the DCGI has not only been empowered but duty bound to automatically monitor any "substance", used in the diagnosis, treatment, mitigation or prevention of any disease or disorder, as a drug and regulate its manufacture and sale to ensure quality. This is clearly stated in very simple language in Section 3, Sub-section b (i) of the Drugs and Cosmetics Act. To make it even clearer, in the same Act medical devices have been defined in Sub-section b (iv) empowering the DCGI to declare them as drugs by a simple notification in the Gazette of India.

Despite these clear clauses, a senior functionary of the DCGI Office had the audacity to issue a letter to importers of stents at unusual haste to say that their wares were not governed by Drugs rules and hence they could be freely imported and sold without permission or licence from DCGI.

It is worth stating that unless an item is deemed to be a drug, its price cannot be controlled by the National Pharmaceutical Pricing Authority (NPPA). Thus by not treating medical devices as drugs, the DCGI had not only enabled importers to bring in sub-standard items but also profiteer by selling them at exorbitant prices, sometimes by offering inducements to prescribers. Such a misconceived interpretation of law was also used by two doctors at J. J. Hospital in Mumbai to test the safety and efficacy of new paclitaxel-coated stents developed by a Singapore-based company on 89 heart patients by using them as human guinea pigs early this year.

When this illegal and unethical clinical trial hit the headlines in the media, a vigilant and upright Commissioner of Maharashtra Food and Drug Administration, M. Ramesh Kumar blew the first whistle. He banned the sale of all unapproved stents in the state. His common sense argument was disarming: even if, just for the sake of argument, it was agreed that normal stents were not "drugs", how can Drug Eluting Stents (DES) escape the provisions of the drug laws? Does a drug cease to be a drug because it is being administered into coronary arteries with stents? Strangely the Office of DCGI decided to disregard this simple logic in support of patients' rights and in the process became the fall guy.

(Courtesy: Editorial in *MIMS India,* October 2005)

Injectablesolutions (or injectables) are sterile preparations of a drug dissolved or suspended in a liquid. Many injectable drugs are packed in sterile disposable syringes to avoid contamination. Some are available in multiple dose vials. They may be administered intramuscularly (through muscle tissue), intravenously (through veins) or subcutaneously (through the skin). Injections can also be intra-articular (injection made within a joint), intrathecal (injection made within the spinal canal), intravascular (within a vessel or vessels), etc.

Suppositories are solid bullet-shaped drug forms which can be easily inserted into the rectum; and when

Efficacy, Safety and Convenience of Dosage Forms

Systemic dosage forms		
Oral		(mixture, syrup, tablet [coated, slow-release], powder, capsule)
sublingual		(tablet, aerosol)
rectal		(suppository, rectiol)
inhalation		(gases, vapour)
injections		(subcutaneous, intramuscular, intravenous, infusion)
Local dosage forms		
skin		(ointment, cream, lotion, paste)
sense organ		(eye drops/ointment, ear drops, nose drops)
oral/local		(tablets, mixture)
rectal/local		(suppository, enema)
vaginal		(tablet, ovule, cream)
inhalation/local		(aerosol, powder)
Oral forms		
Efficacy	:	(-) uncertain absorption and first-pass metabolism (that is, a drug may be metabolised before it can be measured in the systemic circulation, one of the causes of low oral bio-availability), (+) gradual effects
safety	:	(-) low peak values, uncertain absorption, gastric irritation
convenience	:	(-) handling (children, elderly)
Sublingual tablets and aerosols		
efficacy	:	(+) act rapidly, no first-pass metabolism
safety	:	(-) easy overdose
convenience	:	(-) aerosol difficult to handle, (+) tablets easy to use
Rectal preparations		
efficacy	:	(-) uncertain absorption, (+) no first-pass metabolism, rectal fast Effect
safety	:	(-) local irritation
convenience	:	(+) in case of nausea, vomiting and problems with swallowing
Inhalation gases and vapours		
efficacy	:	(+) fast effect
safety	:	(-) local irritation
convenience	:	(-) need handling by trained staff
Injections		
efficacy	:	(+) fast effect, no first-pass metabolism, accurate dosage possible
safety	:	(-) overdose possible, sterility maybe a problem
convenience	:	(-) painful, need trained staff, more costly than oral forms
Topical preparations		
efficacy	:	(+) high concentrations possible, limited systemic penetration
safety	:	(-) sensitization in case of antibiotics, (+) few side-effects
convenience	:	(-) some vaginal forms difficult to handle

Source: *Guide to Good Prescribing*, WHO Action Programme on Essential Drugs, Geneva, 1995. Available at <http://www.who.int/medicines/library/>

these drug forms are available for insertion into the vagina, they are called *pessaries*. They both contain a drug and an inactive substance which is derived from vegetable oil or cocoa butter. The active ingredients are released slowly as the suppository or pessary dissolves at body temperature.

Drops for eyes, ears and nose are drug solutions administered by means of a dropper.

NasalSpray contains a solution of a drug in water administered in the nose by means of a dropper or spray.

Inhalers are drugs in solution or suspension form which are then released under pressure. The aerosol inhalers function by means of a valve mechanism which ensures delivery of the recommended dosage. It contains a mouth piece and is used for respiratory conditions.

2. Evaluation of Drug Profiles

The drug profiles in this book in Section 2 give detailed information on 51 individual drugs. The drugs have been so selected that they cover all the main drug classes which are widely used. When a certain drug-class comprises a number of different drugs, only the ones that are most commonly used have been included in this book.

The drug profiles are aimed at providing information and guidance to the lay person. Information on 107 other drugs has been included in tabular form in Section 3.

Each drug profile is presented in the same way, using standard headings in a uniform sequence. To help the reader understand the information, each heading of the drug profile is explained in detail.

2.1 Name of the Drug

Each drug has got three names. First is the generic name which is the official medical name for the basic drug chosen by scientists, pharmacologists and doctors. The main heading of the drug profile is the generic name of the drug. Rarely does a drug have two generic names - for example, paracetamol is also known as acetaminophen. In such a case, the less commonly known generic name is listed under 'Other Names'.

Then there is the brand (or proprietary) name of the drug, chosen by the manufacturer. Thus there are different brands by different manufacturers but of the same generic drug, available in the market. The differences between various brands are very little. A drug may be available as a generic, as a brand name product, or both. Some brand name products contain more than one generic drug. They are combination products. We do not for the most part give the equivalent brand name products (single and combination, if any) of generic drugs covered in this book, unless they are really well known by non-doctors. Examples of irrational combinations will be found in Chapter 3, Appendix 1, along with reasons for their irrationality.

Example:	*Brand*	*Generic*
	Crocin	Paracetamol
	Brufen	Ibuprofen

Finally, there is the chemical name of a drug which describes it technically, for example, the chemical name of aspirin is acetyl salicyclic acid.

We have not mentioned chemical names in the drug profiles of this book.

2.2 Drug Class

Drugs may be classified in different ways. One way is to classify them according to their chemical similarity, for example, the benzodiazepines. Then, another way is to classify them according to their use, for example, Antimalarials; or according to biological effect, for example, Diuretics. Besides these ways, they can also be classified according to their legal status, for example, Schedule H drugs, Schedule X drugs, etc.

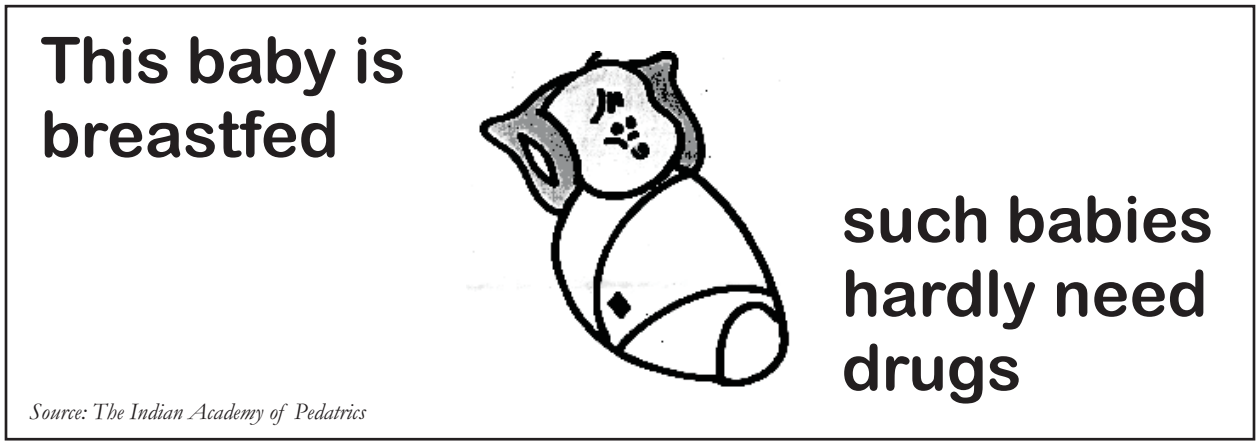
In this book, we have classified the drugs according to their use. Most drugs fit into one class. For those drugs which have multiple uses, all the drug-classes into which they fit are mentioned, for example, for metronidazole, the following drug classes are mentioned: Antiprotozoal, Antibacterial.

One must recognise the class of the drug, one is taking because many properties, effects, interactions with other drugs, etc., are often shared by drugs of the same class.

Almost all drugs given in this book are *prescription drugs*, that is they require a doctor with a minimum of an MBBS degree to prescribe them. Non-prescription drugs are also called OTC (over-the-counter) drugs. For more discussion on OTC drugs, see the box below.

Drugs available on prescription, or prescription drugs, are to be used under medical supervision. They are listed under Schedules H and X of the Drugs and Cosmetics Act, 1945. Your doctor may write the generic name or brand name of a drug in your prescription. Generic products are usually cheaper than brand products.

It is not legal for doctors of one system of medicine to prescribe medicines of another system of medicine. Prescription by allopathic doctors of Ayurvedic, Unani, Siddha or homeopathic drugs shall render such doctors liable to prosecution under both civil and criminal laws resulting in cancellation of registration and/or heavy fine and/or imprisonment.



Prescription Terms: Below is the list of terms which are usually used by a doctor while writing a prescription:

ac	:	before meals	pc	:	after meals
ad lib	:	freely	PM	:	evening
AM	:	morning	bid	:	twice a day
po	:	by mouth	prn	:	once a day
c	:	with	qds	:	four times a day
cap	:	capsule	s	:	without
cc	:	cubic centimetre	sig at diet	:	take as directed
ext	:	for external use	stat	:	at once
ftt	:	drops	tab	:	tablet
mg	:	milligrams	tds	:	three times a day
ml	:	millilitre	top	:	apply topically
node	:	at night	x	:	times

Doctors generally tend to make mistakes in prescription writing. See box below for some common errors and the "Recommendations to Enhance Accuracy of Prescription Writing". It is useful to know what errors doctors make in prescription writing.

Recommendations to Enhance Accuracy of Prescription Writing

Adopted Sept. 4, 1996

Revised June 2, 2005

Personnel to whom this applies: Prescribers; Nursing or Pharmacy staff (who transcribe verbal prescription orders or rewrite transfer or admission orders when entering or leaving a health care facility); Health care administrators/ managers.

Technology plays an important role in the delivery of healthcare. Utilize technology, as appropriate, but evaluate its effectiveness on an ongoing basis. While technology can reduce medication errors and enhance patient safety, it also has the potential to cause new types of unintentional errors.

The Council recommends:

1....all prescription documents be legible. Verbal orders should be minimized. (See the Council's Recommendations to Reduce Medication Errors Associated with Verbal Medication Orders and Prescriptions)

2. ...prescription orders include a brief notation of purpose (e.g., for cough), unless considered inappropriate by the prescriber. Notation of purpose can help further assure that the proper medication is dispensed and creates an extra safety check in the process of prescribing and dispensing a medication. The Council does recognize, however, that certain medications and disease states may warrant maintaining confidentiality.

3....all prescription orders be written in the metric system except for therapies that use standard units such as insulin, vitamins, etc. Units should be spelled out rather than writing "U." The change to the use of the metric system from the archaic apothecary and avoirdupois systems will help avoid misinterpretations of these abbreviations and symbols, and miscalculations when converting tometric, which is used in product labeling and package inserts.

4....prescribers include age and, when appropriate, weight of the patient on the prescription or medication order. The most common errors in dosage result in pediatric and geriatric populations. The age (and weight) of a patient can help

dispensing health care professionals in their double check of the appropriate drug and dose.

5....medication orders include drug name, exact metric weight or concentration, and dosage form. Strength should be expressed in metric amounts and concentration should be specified. Each order for a medication should be complete. The pharmacist should check with the prescriber if any information is missing or questionable.

6....a leading zero always precede a decimal expression of less than one. A terminal or trailing zero should never be used after a decimal. Ten-fold errors in drug strength and dosage have occurred with decimals due to the use of a trailing zero or the absence of a leading zero.[1]

7....prescribers avoid the use of abbreviations including those for drug names (e.g., MOM, HCTZ) and Latin directions for use. The abbreviations in the chart below are found to be particularly dangerous because they have been consistently misunderstood and therefore, should never be used. The Council reviewed the uses for many abbreviations and determined that any attempt at standardization of abbreviations would not adequately address the problems of illegibility and misuse.

8....prescribers avoid vague instructions such as "Take as directed" or "Take/Use as needed" as the sole direction for use. Specific directions to the patient are useful to help reinforce proper medication use, particularly if therapy is to be interrupted for a time. Clear directions are a necessity for the dispenser to: (1) check the proper dose for the patient; and, (2) enable effective patient counseling.

Abbreviation	**Intended meaning**	**Common Error**
U	Units	Mistaken as a zero or a four (4) resulting in overdose. Also mistaken for "cc" (cubic centimeters) when poorly written.
µg	Micrograms	Mistaken for "mg" (milligrams) resulting in an overdose.
Q.D.	Latin abbreviation for every day	The period after the "Q" has sometimes been mistaken for an " I, " and the drug has been given "QID" (four times daily) rather than daily.
Q.O.D.	Latin abbreviation for every other day	Misinterpreted as "QD" (daily) or "QID" (four times daily). If the "O" is poorly written, it looks like a period or "I."
SC or SQ	Subcutaneous	Mistaken as "SL" (sublingual) when poorly written.
T I W	Three times a week	Misinterpreted as "three times a day" or "twice a week."
D/C	Discharge; also discontinue	Patient's medications have been prematurely discontinued when D/C, (intended to mean "discharge") was misinterpreted as "discontinue," because it was followed by a list of drugs.
HS	Half strength	Misinterpreted as the Latin abbreviation "HS" (hour of sleep).
cc	Cubic centimeters	Mistaken as "U" (units) when poorly written.
AU, AS, AD	Latin abbreviation for both ears; left ear; right ear	Misinterpreted as the Latin abbreviation "OU" (both eyes); "OS" (left eye); "OD" (right eye)
IU	International Unit	Mistaken as IV (intravenous) or 10(ten)
MS, MSO4, MgSO4	Confused for one another	Can mean morphine sulfate or magnesium sulfate

Source: © 19982005 National Coordinating Council for Medication Error Reporting and Prevention., USA. See <http://www.nccmerp.org/council>.

2.3 OTC Drugs

These are drugs for which a prescription is not needed, and which are widely available at provision stores as well as at chemist shops. These medicines are usually used for self-treatment and hence should be used only as directed, because, like all medicines, they can be harmful, if misused. Most top-selling drugs in the OTC market are ointments and balms, analgesics and cold preparations, antiseptic creams, cough products, etc. even as the scientific rationality of many of them is questionable.

One must follow the directions given on the label properly and consult the doctor if the symptoms persist even after taking these drugs. It is also advisable to consult your doctor before buying OTC drugs for children. Try to buy a single drug product as far as possible. (Only 12 combination products are rational according to WHO - see Chapter 3).

The phrase OTC Drugs has no legal recognition. To quote a retired Commissioner of Drugs of Gujarat,"OTC Drugs have to be identified by *reductio ad absurdum* logic. It may be said that the current drug laws specify prohibitions - drugs which must not be given without a valid prescription....What is not prohibited is permitted." (See the box.)

Formulations containing drugs not mentioned in Schedules G (to be taken only under medical supervision), Schedule H (list of prescription drugs) and Schedule X (list of narcotic drugs) would appear to deserve the title of OTC drugs (Schedules refer to the Drug and Cosmetics Rules, 1945.). However any move to include a larger number of drugs under OTC must first consider its safety profile, whether drug labels are available in the local language(s), whether children's dose are indicated and whether some Pharma lobby wants to make it an OTC drug merely to increase sales. It is very debatable whether the price of drug will fall because it is made an OTC drug - this is one of the arguments offered by Pharma companies.

OTC Drugs: Some Legal Aspects

'OTC Drugs' in common parlance means drugs which are legally allowed to be sold Over the Counter without the prescription of a Registered Medical Practitioner. The term is clumsy and creates a wrong impression about the official status of the drugs. In India, import, manufacture for sale and the sale and distribution of drugs and cosmetics is regulated by the Drugs and Cosmetics Act, 1940 and its subordinate legislation Drugs and Cosmetics Rules, 1945. The phrase 'Over The Counter' and its abbreviation 'OTC' preparations have no legal recognition and are better referred to as 'non-prescription drugs' and/or as 'household remedies'.

Identification of OTC Drugs: *Since the phrase has no legal recognition, OTC drugs have to be identified by reductio ad absurdum logic. It may be said that the current drug laws specify prohibitions - drugs which must not be given without a valid prescription. What is not prohibited is permitted. Thus, all the drugs which are not specified in the list of 'prescription drugs' must be considered as non-prescription drugs (or the OTC drugs).*

Identification of 'Prescription Drugs': *'Prescription drugs' fall under two schedules of the Drug Rules, 1945 - Schedule H and Schedule X. The latter consists of habit forming, abusable drugs requiring double prescription.*

The containers of the preparations containing Schedule H or Schedule X drugs must conspicuously display on the label the following warning: "*To be sold by retail on the prescription of a Registered Medical Practitioner only*"

The left top corner of the container is marked by any one of the following symbols:

a) " ℞ for - Preparations containing Schedule H drugs.

b) " **N**℞ (in red colour) for - Preparations containing Schedule H drugs which also come within the purview of the 'Dangerous Drugs Act'.

c) "**℞** (in red colour) for - preparations containing Schedule X substances.

Some preparations are not included in Schedule H or X. Yet, in public interest, administrative instructions are given to the manufacturers that their labels carry the same warning as for Schedules H or X viz**.** "*Warning: To be Sold by Retail on the Prescription of a Registered Medical Practitioner Only*".

There are yet some preparations, though available without prescription, contain Schedule G substances. They need to have a cautionary note as follows - "*Caution - it is dangerous to take this preparation except under medical supervision*".

Premises for the Sale of Drugs: There are three types of licensed premises and they display on the board the appropriate description viz. (a) pharmacy/pharmacist/dispensing chemist/pharmaceutical chemist, (b) chemists and druggists or (c) drug store.

(a) Pharmacy/Pharmacist/Dispensing Chemist/Pharmaceutical Chemist*: In such premises -*
i) Pharmacy is maintained for compounding against prescriptions.
ii) Supervision of a qualified person is obligatory.
iii) All types of drugs (OTC as well as prescription drugs) are supplied.

(b) Chemists and Druggists *: In such premises -*
i) Pharmacy is not maintained, so compounding is not permitted
ii) Supervision of a qualified person is obligatory
iii) All types of drugs (OTC as well as prescription drugs) are supplied.

(c) Drug Stores*: In such premises only non-prescription drugs (OTC* drugs) are available. Services of qualified person are not obligatory. Supply of prescription drugs and compounding is not permitted.

DecisionMakers

The Drugs and Cosmetics Rules 1945 can be amended by the Government of India. A draft of amendment along with reasons are prepared by the Government (Drugs Controller of India) and sent for approval of the Drugs Technical Advisory Board (DTAB). After approval of the Board, it is approved by the Ministries of Health and Law. It is then published in the Gazette notification and suggestions invited from those affected by it. Suggestions are considered and if required, the rules amended suitably.

The DTAB has thus a crucial role to play in the process of amendment, as its approval is obligatory. If prior approval is not possible in emergency cases, then the approval of the board has to be taken within six months. The board consists of eighteen members of which five are from the medical profession. These five are:

1. Director General of Medical and Health Services, Ministry of Health and Social Welfare, Government of India.
2. President of Medical Council of India.
3. One person elected by the Central Council of the Indian Medical Association.
4. One person elected by the Executive Committee of the Medical Council of India (from amongst teachers in Medicine or Therapeutics)

.5. One pharmacologist elected by the Governing Body of the Indian Council of Medical Research.

-M.R. Shastri, Director (Retired), Drugs Control Administration, Gujarat.

(Reproduced from: *Bulletin of the Society for Rational Therapy,* July 1991)

2.4 Principal Uses

It lists all the principal disorders/diseases for which the drug is used. It also discusses in brief the main advantages and disadvantages of using the drug. It also includes information on the use of the drug along with other drugs for producing beneficial effects. It may sometimes (when important) also mention certain

circumstances/disorders, for which a drug should not be used.

2.5 How this Drug Works

It tells you how a drug exerts its action once it enters the human body. A drug acts on various parts of the body, sometimes curing the disease while sometimes just relieving the symptoms. Although different drugs act in different ways, their mechanism of action falls in any one of the following three categories:

1) Actionagainstmicro-organisms(germs)thatattackthebodyorabnormalcells

Various micro-organisms such as viruses, bacteria, protozoa and fungi attack the body, causing infectious diseases. Some drugs can kill these micro-organisms or stop their multiplication/growth in the body and thus cure the disease.

Certain diseases such as cancer are caused due to abnormal cells. Some drugs treat such diseases by killing the abnormal cells.

2) Replacementofessentialchemicalsinthebodythataredeficient

The human body needs certain vitamins and minerals to function properly. It obtains them from a balanced diet. If for any reason, the body does not get the essential vitamins/minerals, various deficiency diseases may occur, for example, iron deficiency causes anemia and Vitamin C deficiency causes scurvy. Such diseases can be cured by replacing the deficient vitamin or mineral.

Similarly deficiency diseases also occur when there is a lack of 'hormones' (chemical substances produced by the body to regulate certain important mechanisms), for example, diabetes occur due to the lack of the hormone 'Insulin'. Such diseases are treated with drugs that replace the hormones or with the hormones obtained from animal or synthetic sources.

3) Interferencewiththecellfunction

Certain drugs alter the way in which a cell acts, that is, they either increase or decrease the cell activity to produce the desirable response. This is achieved in different ways by different drugs. In general, there are two ways of interfering with the cell activity:

(a) Certain hormones (chemicals) act on the cells to produce undesirable effects. Some drugs either block the action or the production of such hormones and treat the undesirable condition (for example, pain is produced due to a chemical prostaglandin. The pain-killers (NSAIDS) block the production of the prostaglandin and thus relieve pain).

(b) Some drugs alter the transmission of the messages from one part (that is, the brain) to another part (where the response is desired). To understand this, let us first understand how a message is transmitted.

Any message first originates in the brain from where it is transmitted through nerves to the appropriate part of the body, for example, the message to contract a particular muscle originates in the brain and is transmitted to the appropriate muscle through nerves.

Now let us understand how the nerves transmit the message. Nerves are made of many nerve cells. The nerve cell

receives the message through its receiving end, the message travels like an electrical impulse through the nerve and reaches its sending end. Here a chemical called 'neurotransmitter' is released which conducts the message across the gap separating it from the adjacent nerve cell. This process is repeated until the message reaches the appropriate part of the body.

Thus it can be seen that 'neurotransmitters' are important chemicals which help in conducting the messages between adjacent nerves. This is where the drugs work. They either enhance or reduce the action of the neurotransmitters and thereby facilitate or prevent the conduction of the message respectively. Thus producing the desirable results.

But how can certain drugs alter the action of the neurotransmitters? Let us understand this in detail. The neurotransmitters bind to special sites called 'receptors' on the surface of the cells and thus initiate a response in the cell. (Cells have different receptors for different chemicals in the body.) Now drugs may act in either of the following two ways to produce their desirable effects:

Agonists

1) Some drugs called 'agonists' bind to the receptors similar to those with which the neurotransmitter binds and thus increase the cell response.

A drug called salbutamol is used to treat bronchial asthma, a condition where the bronchial muscles contract causing difficult breathing. The sympathetic neurotransmitter released at this site (bronchial muscles) encourages muscle relaxation. Hence when a drug like Salbutamol which is an 'agonist' to the sympathetic neurotransmitter is administered, it occupies the receptors similar to the sympathetic neurotransmitters and thus enhances its action of muscle relaxation thus decreasing the feeling of breathlessness during the asthma attack.

Antagonists

2) Some drugs occupy the same receptors which the neurotransmitter occupies by displacing the latter (that is, the neurotransmitter) and thus, block the action of the neurotransmitter.

Such drugs are called 'antagonists'.

A sympathetic neurotransmitter called noradrenaline released at the site of heart causes increase in the force and speed of the heart beat. This is not desirable in conditions like hypertension (high BP), angina (heart pain, etc.) Hence in such conditions a drug like propranolol, that is, a beta-blocker, is used. This is an antagonist to noradrenaline that is, it occupies the same beta-receptors as noradrenaline by displacing the latter and thus blocks noradrenaline's action resulting in a decrease in the force and speed of the heart beat.

2.6 Dosage and Usage Information

UsualDoseorDosageRange

Dose of the drug implies the amount of drug to be taken to produce the beneficial effect but not cause excessive harmful effects. If the dose is too low, it may not have any effect at all; if it is too high, it may not produce any additional benefits but may produce adverse effects. This means that the dose should be in the optimum range, somewhere in between the 'No effect' and 'Harmful' effect regions.

This range which is called the 'therapeutic range', varies for different drugs, for example, the drug digitalis

has a very narrow therapeutic range and hence their dose has to be calculated accurately to achieve the desired beneficial effect, while certain drugs like penicillin antibiotics have a very wide therapeutic range and hence their dosage can vary a lot (depending on the infection for which they are used) without changing their effects. This should explain why for certain drugs the dose is mentioned as one specific dose (for example, 200 mg twice daily) whereas for certain drugs, dose is mentioned as a range, for example, 200-500 mg twice daily. The dose of a drug is dependent on factors such as age, weight and general health of the patient.

Age

The amount of medicine required by a patient is dependent on the age of the patient. Children weigh lesser than adults and hence they require lesser amount of drugs. Besides, their metabolic activity (action of liver on drugs to break down) is not as developed as the adults, nor is their excretory power (throwing out waste matter) as powerful. Hence the dose of a drug for children is very small as compared to adults. Children cannot simply be given a proportion of an adult dose as if they were small adults. Dosage has to be properly calculated considering the age and weight of the child.

The more accurate way of giving dosage of a drug for children would be to give it in the form: mg of drug/kg body weight of child. Giving the dose only on age basis would not be very accurate because two children of the same age may have quite a difference in their weights.

A premature baby (baby born before the full-term of nine months) may require higher doses of a drug initially. This is because the amount of water present in the body of a premature baby is high compared to the normal full-term baby, and hence certain drugs are not as concentrated in the premature baby as in a full-term baby. Likewise, doses for older people have also to be adjusted initially. Elderly people are more prone to adverse effects because their liver and kidneys are not as efficient as those of a normal adult. Besides they are not able to comply with the treatment properly on their own and need special attention.

Prescribing for Children: Is a Drug Required?

This question may be difficult to answer, whether the drug is for specific treatment or for symptomatic relief. Drugs are often used in children for self-limiting conditions and for symptoms for which drug efficacy has not been established.

Problem areas include:

(a) antibacterial drugs used for upper respiratory tract infections that are usually viral;
(b) the overuse of decongestants for upper respiratory tract congestion, causing unacceptable adverse effects;
(c) the use of drugs in diarrhoea;
(d) the use of oral anti-emetics for vomiting;
(e) the use of antipyretic agents for fever;
(f) tricylic antidepressant drugs used for nocturnal bed-wetting (these account for three quarters of deaths in children due to accidental poisoning);
(g) the sedation of sleepless children or those falsely labelled hyperactive;
(h) the use of spasmolytics in abdominal pain;
(i) the use of drugs to increase appetite; and
(j) the use of "prophylactic" immunoglobulins for small children with frequent upper respiratory tract infections.

In sum, these areas of drug use account for about 70 per cent of all medicines taken by children, and therefore as much as two thirds of all drugs used by children may have little or no value. The medicalization of some presenting problems and the inappropriate use of drugs for other conditions may have important consequences for future prescribing in terms of parents' demand for and expectation of drug therapy. *The psychological and social consequences for the child given drugs in this way are not known, but children may tend to grow up believing that drugs are the solution to many of life's problems.*

Source : *Drugs for Children.* WHO Regional Office for Europe, Copenhagen, 1987

Weight

The dosage of a drug also depends on the weight of the patient. Doses are calculated considering the average adult human-weight as 70 kg. Although the adult dose for most of the drugs can be generalised and hence the same dose is recommended for all adults irrespective of their age, for certain drugs it becomes very essential to mention dose as mg/kg body weight because giving incorrect doses of such drugs may either produce 'no effect' or 'many harmful effects'.

GeneralStateofthePatient

Another important factor on which the dose of the drug depends is the general state or health of the patient.

Long-term illnesses affect the way in which people respond to drug treatment, especially if a person has a kidney/liver disorder.

Liver is that organ in the human body which breaks down (metabolises) the drug into simpler substances. If the liver is not functioning properly, the 'break down' process is affected and drugs get accumulated in the body. Accumulation of certain drugs leads to dangerous effects. Hence a person with liver problems is prescribed fewer drugs and in lower doses. Besides drugs that cause liver damage (as an adverse effect) are not prescribed for patient who already have liver problems.

People with poor kidney function are also at a greater risk from drug side-effects. Kidney excretes (throws out of the body) the drugs in urine. Obviously when the kidney is not working properly, a lesser amount of drug is excreted while a major portion remains in the body causing harmful effects. Besides this when a kidney is not functioning properly, the number of proteins in the body decreases. There are certain drugs which bind to proteins and such drugs (in free-form/unbound form) increases as the amount of protein decreases, leading to harmful effects. Also care should be taken that drugs with kidney damage as an adverse effect should not be given to people with kidney problems.

It is hence very important for a person to tell his doctor about his/her kidney or liver problems (in case s/he has any) so that the doctor can prescribe the right drug in the right dose for him/her.

Frequencyofdoses

Some drugs produce a very rapid effect while some drugs produce its effect after a long period causing anxiety to the patient. Similarly the effect of certain drugs lasts for a very short time while certain drugs exert their effect for a longer period. The frequency of doses, that is, the number of times a dose has to be taken depends on these factors and is hence different for each drug ranging from taking a dose every few hours to taking it every few days.

Certain drugs like pain-killers or anti-migraine drugs can be taken as and when the need arises while certain drugs have to be regularly taken as per the frequency mentioned. To understand the importance of taking the drug at regular intervals, let us first understand the fate of a drug once it enters the body.

Once a drug enters the body it passes through the digestive tract and reaches the small intestine. From here it enters the blood stream and goes to the liver. In the liver it is broken down to simpler forms which can be easily dispersed throughout the body via blood. The simpler form of drug exerts its beneficial effect only when its concentration reaches a certain level. This level is specific for some drugs and a range for some. After this the drug is excreted from the body by the kidney via urine. As the drug is excreted, concentration

falls below the level required to produce the beneficial effect and thus the effect ceases. It is hence very important to maintain that level constantly. Another dose of the drug is therefore given after a certain time so that the drug undergoes all the various process and is dispersed throughout the body and reaches the required level by the time the previous dose is excreted. This way the level of drug concentration required for beneficial effect is maintained throughout the treatment. If the next dose is not taken after a regular interval, that is, if it is taken after a long gap, the optimum level of drug concentration falls, the effect ceases and the drug therapy will not work well. If the interval is too short, the drug (concentration) level increases leading to harmful effects.

Usually the frequency of a dose is mentioned as the number of times the dose is to be taken, for example, 200 mg 4 times a day. This usually means that the drug is to be taken at four equal intervals during the waking hours, that is, morning, lunchtime, late afternoon and bedtime. However in very rare cases it may be necessary to take the drug at equal intervals during the entire day (24 hours). When it is not necessary to take a drug at specific regular intervals, a range, for instance 2-3 times daily, may be mentioned. When a drug is to be taken only on occurrence of the symptoms, for example pain-killers, frequency is mentioned as 'to be taken as and when required'.

Many diseases are self limiting

nature cures them

DRUGS ARE RARELY NECESSARY

Source: The Indian Academy of Pediatrics

2.7 How to Use/Take this Drug

Specific instructions are given in this column regarding the use of the drugs.

For oral medicines (those taken by mouth), it is very important to follow the instructions regarding the intake of food, to get the maximum benefit of the drug. Certain drugs should be taken on empty stomach, that is, one to two hours before food, so that they get into the blood more quickly while others are to be taken with food so that they do not cause stomach irritation. Besides this, the instructions regarding avoiding certain foods which may impair the drug's action should be followed, for example, milk and dairy products inhibit the action of tetracycline and should therefore be provided in patients, taking tetracycline. Similarly, one must also follow advice about taking certain foods with certain drugs as supplements of vitamins and minerals, for example, with diuretics sometimes the patient may be advised to eat foods rich in potassium.

Tablets should be swallowed whole (unless advised to take half a tablet). Capsules may be opened and the contents can be swallowed if the patient finds it difficult to swallow the whole capsule. If possible swallow tablets and capsules in a upright sitting position/standing position with at least half glass of water. This helps the medicine to act much faster.

Liquid medicines should always be taken, after shaking the bottle properly, or else it may cause inaccuracy of doses in case the drug has settled at the bottom of the bottle. The doses should be measured carefully especially for children, accurately marked droppers should be used for measuring the dose.

Specific instructions for the use of other dosage forms, for example, skin preparations (ointment, cream, lotion), eye drops, inhalers, etc., are given in individual drug profiles and should be followed accordingly.

A variety of specialised dosage forms, for example, aerosol sprays, transdermal patches, slow release capsule, suppositories, etc., are available in the market. There are special instructions for the use of such dosage forms which are also mentioned where necessary under individual drug profile.

One should always remember that the most important aspect of drug treatment is the way one take or uses the drug, that is, in the correct dose at the right time and in compliance with all the instructions for its use.

2.8 What if You Miss A Dose

To miss a drug dose is not an unusual phenomenon and is neither considered to be of any concern in case of most of the drugs. It can only be a problem if the drug has to be taken regularly for a long time.

The frequency of doses will depend on how long the action of the drug will last. When a dose is missed, the amount of level of drug required for beneficial effect falls and the drug-effect ceases. This may, sometimes lead to unwanted effects, for example, if a woman is taking oral contraceptives (which are to be taken regularly for 21 days) and forgets to take the pill for a few days, she may become pregnant. Other important examples of drugs with which missed doses may produce return of symptoms or alter the effects of drugs are insulin, anti-epileptics, etc. In such cases, it is very important for the patient to know what to do if he/she misses a dose. This advice is mentioned in the profiles of these drugs where missed dose may

cause problems. For those drugs with which missed doses are not of concern this column is omitted altogether.

2.9 How to Stop Using this Drug

The way one ends a drug treatment is very important in the case of drugs to be taken regularly for a long time. One can end the drug treatment on feeling better if one is on drugs which are to be taken as and when required. The advice for stopping the drug is given in this column only in those drug profiles where it is necessary. Usually people tend to stop drug treatment on their own once they begin to feel better or if they experience many adverse effects of the drug.

This should not be done.

It does not mean that a disease/disorder is cured if the symptoms no longer appear. One should not stop taking the drug without the doctor's advice even if one begins to feel better. The full course of treatment should always be completed, especially for drugs like antibiotics (drugs used to treat infections).

Most of the drugs tend to cause side-effects which may be very unpleasant at times. Many of these disappear or become tolerable after some time. Thus the occurrence of side-effects does not imply that the drug treatment should be stopped. Of course, it may be necessary to do so in some cases and hence one should check with the doctor if one experience side-effects of a drug. The doctor may change the dose or the drug

2.10 Gross Overdosage

Many times people have this false belief that if they take an additional amount of drug than what is prescribed, they will experience a faster effect or a better/effective cure. There are others who exceed the dose by mistake. This is especially true for elderly people who take the dose twice, forgetting that they had already taken a dose before. Some cases of overdosage may also occur when the dose is exceeded intentionally as a suicide attempt or when children take large amounts of drugs just because they find it to be an interesting/attractive item. Whatever the reason for overdosage, one should always be conscious enough to notice any unusual symptoms that may occur during drug treatment and report to the doctor immediately whenever necessary.

Taking a single extra dose occasionally may not pose much of a problem for most of the drugs but several overdoses may create a lot of unwanted effects which appear immediately or after a few days and may lead to dangerous consequences. However, for drugs with a narrow therapeutic range, even the slightest amount of extra dose may cause dangerous effects.

What happens in case of gross overdosage of a drug and what should be done in that case is mentioned in this column only under those drug profiles where necessary.

People with impaired liver or kidney functions should be extra careful not to exceed a prescribed dose. In such people the break-down process (by liver) and the excretion process (by kidneys) are not as efficient as in normal patients, and this may cause accumulation of drugs in the body leading to dangerous side

effects.

Similarly elderly people and children should be well-cared for so that they do not take many extra doses.

For Poisoning and its Treatment see end of this Chapter, Annexure 2.

2.11 Precautions

It is very important that you give all relevant information about yourself to your doctor. This helps the doctor to prescribe the drugs rationally and also reduces the chances of adverse effects of the drug. The points to be discussed with your doctor varies as the disease/disorder as well as the drugs used for treatment vary. This column lists down all the relevant points that must be communicated to the doctor who is prescribing that drug. However, there are certain general points which must always be told to the doctor, no matter what the drug is or the disease/disorder under consideration. They are as follows:

- Tell your doctor about any other drugs you are taking already.
- Tell your doctor if you are pregnant or intend to become pregnant.
- Tell your doctor if you are breast feeding
- Tell your doctor if you have or have had in the past any specific health problem such as liver or kidney disease or any other severe disease/disorder.
- Tell your doctor if you have to undergo any kind of surgery in the near future.
- Tell your doctor if you are on any kind of special diet, for example, low-sugar or low-salt.
- Tell your doctor if you have had allergic reactions to any past treatment.

Pregnancy

The most important rule when you are pregnant or intend to become pregnant is to consult your doctor before taking any kind of medicine, either prescription or OTC.

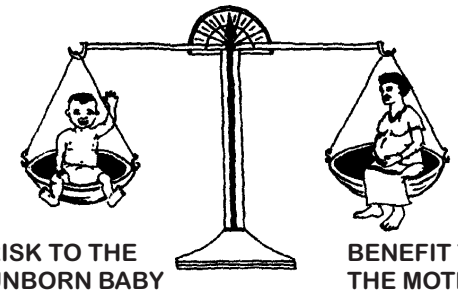
Many drugs are known to cross the placenta (barrier between the mother's and the baby's blood streams) and cause adverse effects on the foetus (developing baby). Some drugs may also adversely affect the mother's health. There are certain drugs which are considered to be safe, but there is no firm proof of their safety and hence it is always better to let your doctor decide whether you should take a particular drug or not.

In some instances, when the pregnant woman is suffering from a chronic condition such as epilepsy, high B.P., diabetes or any kind of severe disease, it may become necessary to give her drug treatment. The doctor then, balances the possible benefits and risks of the drug and decides if it should be taken or not. It is always preferable to avoid drugs for minor ailments. Drugs such as marijuana, nicotine (tobacco) or alcohol should also be avoided.

Effect of Drugs During the Different Trimesters of Pregnancy

The nine month old period of pregnancy is divided into three stages, each of three-month duration. These three stages are called trimesters. A drug may exert different effects on the mother or the foetus or both

depending on which trimester of pregnancy, it is being used. The first three months or the first trimester of pregnancy is the most critical period. Certain drugs may adversely affect the development of organs in the foetus. Very severe defects may result in miscarriage. During the second trimester, the drugs may retard the growth of the foetus, which can also cause a low birth weight. Drugs taken during the third and last trimester may cause breathing problems in the newborn baby or may cause premature/delayed birth.



Source: Practical Pharmacy

Drugs to be Avoided or Used with Caution During Pregnancy

Some drugs are dangerous throughout all months of pregnancy. The table below lists drugs which definitely should not be given during pregnancy and those which are best to avoid if possible.

Drug	Avoid	Caution	Comments
Antibiotics			
Chloramphenicol		3	Avoid using long courses. Causes 'grey' baby syndrome.
Co-trimoxazole		3	Can cause abnormalities and blood disorders in the baby.
Gentamicin		1,2,3	Only use if really necessary
Griseofulvin	1,2,3		Use topical drugs if really necessary
Metronidazole	1	2,3	Use lower doses (see following page for more details)
Nitrofurantoin		3	May affect the baby's blood if used near to delivery
Streptomycin	1,2,3		Can damage hearing of the baby. Note: treatment for TB should not be interrupted or postponed during pregnancy. Refer to your national TB guidelines for drugs of choice in pregnancy. If isoniazid is used, pyridoxine should also be given to prevent peripheral neuropathy.
Tetracyclines	1,2,3		This includes doxycycline.
Anti-malarials			
Halofantrine (Halfan)	1,2,3		
Mefloquine (Lariam)	1	2,3	Only use if no other drug is available.
Pyrimethamine/ Sulfadoxine (Fanisdar)		1,2,3	If possible use quinine instead
Quinine			This benefit outweighs the risk. Preventive measures are very important such as sleeping under a net and taking prophylaxis, e.g. chloroquine each week.
Antihelmintics			
Albendazole	1,2,3		Known to cause abnormalities in animal studies.
Mebendazole	1	2,3	Consider using piperazine if appropriate
Praziquantel		1,2,3	If possible wait until after delivery

Thiabendazole	1,2,3		Although thiabendazole is no longer on the WHO essential drug list, it may still be widely used.
Analgesics			
Aspirin & other NSAID	3	1,2	Use paracetamol
Anti-epileptics			
Carbamazepine		1,2,3	Benefit outweighs the risk.
Phenobarbitone		1,2,3	If possible use only one
Phenytoin		1,2,3	Use drug and monitor blood levels.
Miscellaneous			
All cancer drugs	1,2,3		Seek specialist help.
Aminophylline/ theophylline		3	May cause irritability in the baby if used near delivery.
Benzodiazepines e.g. diazepam		1,2,3	Avoid regular and prolonged use.
Iodine	1,2,3		High doses can cause goitres in the baby.
Vitamin A (Retinol)	1		Large doses may cause abnormalities in the 1st trimester.

1 = first trimester (1-3 months) 2 = second trimester (4-6 months) 3 = third trimester (7-9 months)
AVOID = do not use at all
CAUTION = only use if the benefit outweighs the risk.
If the drug is not listed above it does not mean it is safe to use in pregnancy. Please check other literature for more information.

Source:*Practical Pharmacy*, April-June, 1998, Issue 9

Breast feeding

Most drugs can pass from the mother's blood stream into the mother's milk just like the way they pass from the mother's blood stream into the baby's blood stream. A baby who is being breast fed will thus receive small amounts of drugs that the mother is receiving.

There are certain drugs which do not pass into the mother's milk at all because of their chemical nature and there are others which do pass into the breast milk but in amounts too small to produce any harmful effects on the baby. However, there are certain drugs which produce unwanted effects on the breastfed baby for reduced milk production in the mother. It is always advisable for the mother to consult the doctor before taking any drug, while breast feeding the baby. One must try as far as possible to avoid drugs rather than avoiding breast feeding. When the mother is suffering from chronic conditions, and has to regularly take drugs, and the doctor decides, if she can continue breast feeding or not. In case she is allowed to continue to breast feed her baby, the baby should be closely monitored (observed) by the doctor for any possible harmful effects. It is important to remember that besides very few chronic conditions a mother is never advised to refrain from breast feeding. Advice on breast feeding varies as the drugs vary and is discussed in this column whenever necessary.

Drugs to be Avoided OR Used with Caution During Breast Feeding*

Drug	Avoid	Caution	Comments
Chloramphenicol		X	Only use if no other antibiotic is suitable.
Ciprofloxacin	X		
Co-trimoxazole		X	Especially if the baby has jaundice.
Metronidazole		X	Avoid large single doses e.g. 2g daily.
Tetracyclines	X		This includes doxycycline.
Others			
Aspirin	X		Use paracetamol instead.
Benzodiazepines e.g. diazepam		X	Avoid repeated doses. May cause weight loss and tiredness in the baby.
Carbimazole	X		May affect the baby's thyroid function.
Cimetidine		X	A significant amount is found in breast milk - not known to be harmful but advisable to avoid using.
Ephedrine		X	May cause irritability and disturbed sleep patterns in the baby.
Iodine (includes cough mixtures with iodine)	X		It appears that iodine is concentrated in breast milk and can severely affect the thyroid gland of the baby. If absolutely necessary to treat the mother then advise to stop breast feeding.
Oestrogens (in oral contraceptives)	X		Reduces the milk supply. Choose an oral contraceptive that contains progesterone only.
Phenobarbitone		X	May cause drowsiness and inhibit the baby's suckling reflex.
Thiazide diuretics e.g. bendrofluazide		X	Large doses may reduce milk supply.

If a drug is not listed in the table it does not mean that it is definitely safe to use. Please check other literature for more details.

*Reproduced with thanks from: *Practical Pharmacy*, April-June 1998, Issue 9

InfantsandChildren

Infants and children have frequent but not usually serious illnesses. A child's frequent illnesses in the early years are part of a natural process which develops his or her immature immune system. These generally mild infections help to build immunity against common diseases. Nutritious food, cleanliness and vaccinations are three important bodyguards that protect children against many diseases.

An important question which arises is that should children be given so many drugs for their illness? The answer is 'No'. However, the fact remains that too many drugs are being given to infants and children although most of them have very little or no value. Besides, subjecting children to lot of drugs means subjecting them to lot of adverse effects.

The main reason for children being more prone to adverse side-effects of drugs is that children are not just small adults. The way a child's body deals with drugs in completely different from that of an adult body.

The organs responsible for the breakdown and elimination of drugs, that is, the liver and the kidney respectively, are less efficient in a child's body than in a adult body. Hence if adult doses of a drug are given to children, drugs get accumulated in their body and produce harmful effects. This is why it is important that accurate doses be calculated for children taking into consideration both their age and weight.

Certain drugs are harmful to children even in therapeutic doses and should be completely avoided, for example, loperamide, tetracycline. Parents should always determine if a drug is really necessary for their child's condition and check if there is any non-drug alternative. They should avoid giving unnecessary drugs to their children who may grow up believing that medicines are solutions to many of life's health problems.

There are many drugs which are commonly misused in children. Some examples are:

* Antibacterials for viral upper respiratory infections.
* Decongestants for colds, resulting in unacceptable adverse effects.
* Drugs to treat diarrhoea.
* Oral anti-emetics for vomiting.
* Antipyretic agents for fever.
* Tricyclic antidepressants for bed wetting.
* Sedatives for sleepless children or those labelled hyperactive.
* Spasmolytics for abdominal pain.
* Appetite stimulants, vitamins and tonics.

Advice on use of individual drugs in children is given in this column wherever necessary.

Guidelines on the Use of Drugs in Children

While administering drugs to children, particularly neonates (first 30 days of life), special care is always needed because they differ from adults in their response to drugs. Doses should invariably be calculated on the basis of weight till 50 kg or puberty is reached. In the neonatal period, the risk of toxicity is higher due to inefficient renal clearance, relative deficiencies of various enzymes, heightened sensitivity and inadequate detoxifying mechanism.

If possible, painful intramuscular injections should be avoided. It is always a good practice to state the age of child patient while writing prescriptions. Even though liquid preparations are more easily accepted by children, many contain sucrose which can lead to dental decay.

Dosage: Children's doses are usually stated in the following age ranges: Neonate (first month), infant (upto 1 year), 1-5 years and 6-12 years. Where a single dose is given, it applies to the middle of the age range. Hence adjustment would need to be made for lower and upper limits of the stated range.

Dose Calculation: The dosage for children can be calculated from adult doses by using either age, or body-weight or body surface area or by a combination of these factors. Even though body-surface area provides the most reliable method of determining dosage, in practice it is exceedingly difficult.

Body-weight can be easily used to calculate doses and are generally expressed in mg/kg. Because of their higher metabolic rate, children generally require higher dose per kilogram than adults. This method can pose problems while calculating dose for obese children since they are liable to be given higher than required dose. Under such circumstances, it is better to calculate dose based on ideal body weight of the child in that particular age.

Body-surface Area (BSA): is technically a better and more accurate method since many physical phenomenon are

more closely related to body-surface area. The average body-surface area of a 70 kg adult is about 1.7 - 1.8 square meter. Thus to calculate the dose for a child the following formula is used:

$$\text{Approximate dose for child} = \frac{\text{Surface area of child } (m^2)}{1.8} \times \text{adult dose}$$

The **Percentage Method** as given below can be conveniently used to calculate doses for children when there is wide margin between therapeutic and toxic dose:

	Ideal body weight	Height	Body-Surface	Percentage of Adult Dose
Newborn	3.4kg	50cm	0.23m	12.5%
1 month	4.2kg	55cm	0.26m	14.5%
3 months	5.6kg	59cm	0.32m	18%
6 months	7.7kg	67cm	0.40m	22%
1 year	10kg	76cm	0.47m	25%
3 years	14kg	94cm	0.62m	33%
5 years	18kg	108cm	0.73m	40%
7 years	23kg	120cm	0.88m	50%
12	37kg	148cm	1.25m	75%

I biotics are usually stated as every 6 hours. In the case of children, some flexibility may b ken up at night. In the case of new drugs, the recommended doses must not be exceed.

Source:*MIMS India,* January 2006. Reproduced with permission.

O

Th gives any special warning/instructions regarding drug use in the elderly (that is e average). Older people are at more risk to the adverse effects of drugs than health problems are more prevalent among the elderly as a result of which s at the same time. Besides, their liver and kidney (organs which break down and eliminate drugs from body respect), are not efficient enough and hence drugs get accumulated in their body producing harmful effects. Hence drugs causing liver/kidney toxicity are not to be used for elderly people.

As people grow older, many physical changes take place in their body, for example, their brain becomes more sensitive to drugs, and their immune system goes weak which means they are more prone to allergic and other unexpected reactions caused due to the drug treatment.

Hence it is very important that the doctor correctly determines the drugs that can be used as well as the dosage regimen to be followed in an elderly person. They are to be regularly observed by the doctor to check if the treatment is working well. If too many drugs are to be given to an old person, the spacing of drugs should be such that they do not interact with each other.

Elderly people are more likely to miss doses, exceed the dose or not follow the dosing instruction carefully. Hence their care-takers should always see to it that they comply well with all the instructions regarding their drug treatment.

Drugs most frequently associated with adverse effects in the elderly: antihypertensives (drugs used for high BP), antiparkinson drugs, corticosteroids, psychotropics, digitalis, insulin and antidiabetics, diuretics.

Guidelines on the Use of Drugs in the Elderly

Special care needs to be taken while prescribing for the elderly due to the following:

- It is not unusual for elderly patients to receive multiple drugs for multiple diseases. This results in increased risk of advertise drug reactions and drug interactions.
- Manifestations of normal ageing process (e.g., giddiness due to loss of postural stability) are commonly mistaken for the existence of disease leading to inappropriate therapy.
- Based on past prescriptions, "friendly advice" from other colleagues, elderly may be already consuming both OTC and prescription-only drugs. This aspect should always be kept in mind.
- A new symptom or sign may not be due to a new disease but the adverse reaction of a drug which is already being taken.
- Ageing nervous system has enhanced susceptibility to commonly used medicines such as analgesics, tranquilisers and anti-Parkinsonian agents.

Pharmacokinetics: Due to a variety of reasons [prostatism (conditions governing chronic disease of prostate gland), nephrosclerosis (a condition involving hardening of kidneys), UTI (Urinary Tract Infection)] renal clearance is reduced. Thus drugs are excreted slowly and elderly patients are at greater risk from nephrotoxic agents. Great care needs to be taken while administering drugs with narrow safety margin between therapeutic and toxic dose such as digoxin. As a thumb rule one should take tissue concentration of drugs to be 50% more in elderly than younger patients.

Adverse Reactions: Many side-effects present themselves in a non-specific manner. Mental confusion, constipation, postural hypotension and falls are common.

Use of hypnotics with long half life should be avoided. Diuretics are over-prescribed in the elderly. They should not be used on long-term basis. Blood disorders caused by drug therapy are much more common in the aged. Therefore drugs which depress bone marrow function, such as co-trimoxazole, mianserin, should not be used unless an acceptable alternative is not possible. Bleeding associated with NSAIDs and aspirin are more common in the elderly.

General Guidelines: One should prescribe drugs to the elderly only when clearly indicated. It is better to prescribe established drugs from a limited range, which have been well tried out and whose effects in the elderly are well known.

Dosage should generally be 50% of the adult dose. Repeat prescriptions should be written only after thorough review. It is often possible to withdraw a drug altogether. Sometimes dosage may need to be tailored to match diminishing renal function.

If possible, no more than three drugs should be prescribed at a time to be taken no more than twice daily. In particular, drug regimens which call for complicated, confusing and different dosage intervals should be avoided.

A close live-in young relative of the elderly should be explained the dosage regimen so that even by mistake the patient does not consume more than medically advised.

Source: *MIMS India,* October 1998. Reproduced with permission.

Others

This column in the drug profile lists down all other precautions and warnings that a person consuming the drug must know. Any specific condition for which the drug must not be used or used with caution, for example, diabetes, heart attack patients, etc., are also listed in this column.

2.12 Possible Adverse and Side-Effects

A drug may cause other several different effects in your body, besides producing the desirable beneficial effect for which it is consumed. These other effects are of two types (although we have listed all of them under the same heading for the sake of convenience): Possible side-effects and Possible Adverse Effects.

PossibleSide-Effects

These effects are natural, expected and usually unavoidable actions of the drug. Whenever a drug is consumed (by any route) it is distributed all throughout the body and not restricted to just one particular organ in the body. Thus a drug produces the desirable effect in one particular organ for which it is taken and undesirable effects in all other organs where it also acts simultaneously. For example, anticholinergic drugs are taken to relieve spasm in the wall of the intestine, but they also affect the eyes causing blurred vision, the mouth causing dryness and the urinary bladder causing retention of urine. All the effects caused in organs other than the intestine are undesirable and will be called 'Side-Effects' of Anticholinergic drugs. Such side-effects disappear slowly as the body gets used to the drug. One must consult the doctor if the side-effects are troublesome or persist for a long period of time. The doctor may change the drug or the dosage regimen so as to reduce the side-effects. Sometimes a patient may have to tolerate the side-effects of certain drugs which are the only available drug for the treatment of their disease - which itself may be very serious and could prove fatal (that is, cause death of the patient) if left untreated, for example, a disease like cancer. In such cases regular and careful observation (monitoring) by the doctor throughout the treatment is necessary. Hence a doctor always evaluates the benefits (therapeutic effects) and risks (possible adverse effects) of a drug treatment before prescribing a drug.

PossibleAdverseEffects

Adverse effects are unexpected, unusual and unpredictable reactions of the drug.

They may be caused because the patient is allergic to the drug or due to some genetic deficiency in the patient such as the lack of an enzyme which inactivates the drug may lead to accumulation of the drug causing adverse reactions. They may also occur due to interactions with other drugs.

Adverse effects may be either mild or serious in nature, which determines the steps one should take if they occur. This column of the drug profile tells you what adverse effects or side-effects to expect once you take a particular drug , how frequently may an adverse/side effect occur and what to do in case it occurs.

One should always be alert to significant changes that occur in one's body while taking drugs especially those drugs which are known to produce adverse effects. One may also experience certain reactions which are not yet reported and hence not listed in this column. In such cases, the doctor should be consulted immediately.

It is important to note that if you consult a rational doctor and inform him/her regarding your medical history in detail, it is most likely that he/she may prescribe the correct drug for you, which is less likely to produce an harmful adverse effects. While it is true that no drug is safe and even the mildest drug can produce serious adverse effects if misused or abused, most drugs will not cause serious harm if used correctly.

Just because a drug can produce certain adverse effects one should not hesitate to use it, when it has been

prescribed by the doctor. The adverse effects of drugs are listed down in this column as a measure of precaution and not to create panic amongst the users.

2.13 Interactions

Whenever a drug is taken along with other drugs or certain foods or alcohol, it is likely that the drug may interact with them and produce effects which are entirely different from those produced when it is taken alone. Many times these interactions may produce beneficial effects which are utilised in the treatment of the patient, for example, for the treatment of high blood pressure, usually more than one drug is prescribed. Other interactions may produce harmful and unwanted effects and hence their occurrence should be avoided. Such interactions may occur not only between two prescription drugs but also between OTC drugs and prescription drugs. It is therefore necessary to read the warnings on the labels of drugs which you are taking and also inform your doctor about all other drugs that you are taking when s/he is prescribing a drug for you. This helps the doctor to choose the right drug for you, which will not interact with other drugs you are taking or at least suggest a dosage regimen where the doses of the two drugs are spaced far enough to avoid an interaction.

ExamplesofImportant(Dangerous)Interactions

(1) Drugs that depress the central nervous system (sleep inducing drugs, narcotics, antihistamines and alcohol). The effect of two or more of these in combination may be additive causing dangerous oversation.

(2) Drugs that lower blood sugar levels and such drugs as sulfonamides and alcohol. The drug interaction increases the effect of blood sugar lowering drugs, thus further depressing blood sugar levels.

(3) Oral anticoagulants and other drugs, particularly aspirin and antibiotics. Because these drugs may increase the tendency to bleed, it is essential to check the effects in every case.

(4) Monoamine Oxidase Inhibitors (MAOIs): There is a large list of drugs and foods which can produce a severe rise in blood pressure when taken with these drugs. Dangerous drugs include amphetamines and decongestants. Foods that interact include cheese, herring, red wine, beer and chocolate.

This column lists down only the important interactions of the drug with other drugs. (Its interactions with food, alcohol, tobacco, etc., are mentioned under 'Precautions'). The final effect of drug-drug interaction is mentioned along with explanatory/warning notes wherever necessary.

I stopped taking the medicine because I prefer the original disease to the side effects.

Drug-Nutrient Interactions

Medication	Use	Effect on Nutritional Status
Alcohol	Toxic effect on intestinal lining, altered secretion of Digestive enzymes	Reduced absorption of vitamin B1, folic acid, vitamin B2, increased excretion of magnesuim and zinc; reduced blood levels of vitamin B12.
Amitriptyline Imipramine Lithium carbonate	Antidepressant	Weight gain; altered blood glucose; increased blood levels of magnesium; increased excretion of calcium.
Amphotericin B	Antifungal	Increased urinary excretion potassium and nitrogen; reduced blood levels of magnesium and potassium.
Antihistamines	Nasal Congestion	Increases appetite
Barbiturates	Anticonvulsant	Increased need for folic acid and vitamin D; reduced absorption of vitamin B1; increased excretion of vitamin C.
Biguanides Metformin, Phenformin	Diabetes	Reduces absorption of vitamin B12.
Chloramphenicol	Antimicrobial	Increased need for vitamin B2, vitamin B6, and vitamin B12.
Chlorpromazine	Tranquilizer	Increased appetite and body weight.
Colchicine	Anti-inflammatory	Reduces absorption of carotene, sodium, potassium, vitamin B12, lactose.
Colocynth	Cathartic	Reduces transit time and absorption of nutrients.
Corticosteroids		Reduced absorption of calcium and phosphorus; increased urinary excretion of vit C, calcium, potassium, zinc, and nitrogen; reduced blood levels of zinc; increased blood levels of glucose, triglycerides, and cholesterol; increased need for vitamin B6, vitamin C, folic acid, and vitamin D; impaired bone formation; reduced wound healing.
Coumarin	Anticoagulant	Antagonist to vitamin K.
Cycloserine	Antitubercular	Reduced protein synthesis; reduced absorption of calcium and magnesium; reduced blood levels of folic acid, vitamin B12, and vitamin B6.
Dextroamphetamine	Appetite suppressant	Weight loss, reduced growth of children.
Indomethacin	Analgesic	Reduced blood level of vitamin C; reduced absorption of amino acids; anemia.
Insulin	Diabetes	Increases appetite
Glutethimide	Sedative-hypnotic	Increased need for vitamin D.
Griseofulvin	Antifungal	Alters taste sensitivity
Hydralazine	Antifungal	Increased excretion of vitamin B6.

Medication	Use	Effect on Nutritional Status
Isotretinoin (a	Acne	Avoid supplementation with vitamin A synthetic derivative of vitamin A)
Jalap	Cathartic	Reduces transit time and absorption of nutrients.
Kaon-Cl	Potassium	Reduces absorption of vitamin B12
K-Tab	Potassium	Reduces absorption of vitamin B12
Klotrix	Potassium	Reduces absorption of vitamin B12
Lithium carbonate	Tranquilizer	Increases appetite and body weight
Methylphenidate	Appetite suppressant	Weight loss and reduced growth in children.
Micro-K	Potassium	Reduces absorption of vitamin B12
Paraaminosali-cyclic acid	Antitubercular	Reduced absorption of vitamin B12, iron, folic acid, and fat.
Penicillins	Antimicrobial	Reduced blood levels of potassium
Phenobarbital Phenytoin Primidone	Anticonvulsant	Impaired vitamin D metabolism; increased excretion of vitamin D; reduced blood levels of folic acid; vitamin B12, and vitamin B6; anemia.
Podophyllin	Cathartic	Reduces transit time and absorption of nutrients.
Propranolol	Cardiac	Reduced glucose tolerance.
Slow-K	Potassium	Reduces absorption of vitamin B12

Source: David Heber et al. *Prescription Drugs and Nutrition*. Health Media of America. Published in India by CBS Publishers and Distributors, Delhi, 1994.

Drug-Nutrient Interactions and Dietary Recommendations

Drug	Effects on Nutritional Status	Dietary Recommendations
Antacids	Bloating, Constipation, nausea. Reduces phosphate, reduces vitamin A, loss of appetite	Take between meals. Increase intake of vitamin A, iron, and folic acid.
Bisacodyl (laxative)	Diarrhea, nausea, fluid loss. Reduces absorption of glucose. Hypokalemia (loss of potassium).	Take on empty stomach with water. Increase water intake.
Cholestyramine (lipid lowering)	Bleaching, bloating, constipation, diarrhea flatulence, stearorrhea (high fat in stools).	Increase intake of fat-soluble vitamins, carotene, iron, B12 B12, and calcium. High fiber diet if constipated.

Drug	Effects on Nutritional Status	Dietary Recommendations
Colchicine (antigout)	Diarrhea, nausea, vomiting. Reduces absorption or increases excretion of sodium potassium, fat, carotene B12, folic acid.	Take with water and food. Avoid alcohol. Increase fluid intake. Supplement or increase dietary intake of high risk nutrients.
Furosemide (Diuretic)	Constipation, diarrhea, nausea, or vomiting. Increased excretion of potassium, calcium, magnesium, sodium, water. Dry mouth, loss of appetite.	Take single dose early in morning.
Hydralazine (antihyper-tensive)	Diarrhea, constipation, nausea. Reduces B6, loss of appetite, and sodium retention.	Take with food. Maintain ideal weight. Vitamin B6 supplemen-tation. Sodium restriction
Isoniazid (anti-tubercular)	Stomach distress, nausea, vomiting. Reduced B6. Dry mouth. Loss of appetite.	Take on empty stomach. Avoid alcohol. Vitamin B6 Supplementation.
Methotrexate (cancer)	Diarrhea, GI bleeding, nausea or vomiting. Reduces folic acid. Poor absorption of B12. Loss of appetite, sore mouth and throat, altered taste.	Increase water intake. Avoid alcohol.
Mineral Oil (laxative)	Flatulence, nausea, vomiting. Reduces absorption of vitamins A, D, E, K. Loss of appetite and weight loss. Hypokalemia (low potassium)	Take 2 hrs before a meal. Increase fat-soluble vitamin intake.
Penicillamine (antiarthritic)	Diarrhea, nausea, vomiting. Reduces copper, zinc, and iron. Altered taste and loss of appetite.	Take with water. Take on empty stomach. B6 and trace mineral supplementation.
Phenolphthalein (laxative)	Reduced absorption of vitamin D, calcium, and other minerals. Hypokalemia (low potassium).	Take on empty stomach. Chew well.
Phenylbutazone (anti-inflammatory)	Constipation, diarrhea, heartburn, fluid retention, and weight gain.	Take with food. Avoid alcohol.
Steroids	Bloating, indigestion, nausea. Fluid and sodium retention. Reduced absorption of vitamin D.Osteomalacia.	Take with food or low-sodium snack. Sodium-restricted diet. Increase potassium.

Drug	Effects on Nutritional Status	Dietary Recommendations
Steroids (anabolic)	Nausea, vomiting, fluid retention, edema, and weight gain.	
Sulfasalazine	Diarrhea, stomach distress, nausea,	Take with water.
(anti-inflammatory)	vomiting. Reduces absorption of	Increase water intake.
	folic acid. Loss of appetite.	Increase folic acid-rich foods.

Source: *David Heber, op.cit.*

The Effects of Food on Absorption and Action of Medications

Food	Drug	Action
Coffee/tea	Neuroleptic agents	Reduces drug absorption
	Theophylline	Increases drug side-effects
Citrus	Quinidine	Increases blood levels of drug
Fiber (bran, Pectin)	Digoxin	Reduces drug absorption.
Food	Drug	Action
Food/meals	Chlorothiazide	Increases drug absorption
	Propranolol	Increases drug absorption
	Nitrofurantoin	Increases drug effectiveness
	Cimetidine	Delays drug absorption
	Aspirin	Reduces drug absorption
	Tetracycline	Reduces drug absorption
High-fat foods	Griseofulvin	Increases drug absorption
High-protein foods	Levodopa, methyldopa	Reduces drug absorption
Licorice	Antihypertensive	Induces hypokalemia and drugs sodium retention
Milk	Tetracycline	Reduces drug absorption
Meal with Milk	Methotrexate	Reduces drug absorption
Salty foods	Lithium	Reduces drug effectiveness
Vegetables (dark green)	Warfarin	Reduces drug effectiveness

Source: *David Heber, op.cit.*

2.14 Effect of Long-Term Use

Many diseases/disorders require long-term drug treatment either to control the symptoms or to prevent them for occurring again, for example, patients with Insulin-dependent Diabetes have to take Insulin regularly for all their whole life. There are certain other diseases/disorders which take a long time to cure, for example, Tuberculosis requires at least six months treatment with drugs.

Certain drugs cause adverse effects, especially on long-term use. If you are regularly taking a drug for a long time, you should know the possible long-term adverse effects of the drug which you should expect. As soon as any of them occur, you should report to the doctor immediately. One must never stop using the drug without consulting the doctor just because of the appearance of adverse effects. Doing so may cause worsening of the symptoms which can sometimes prove more dangerous than the adverse effects of the drug.

The possible adverse effects that may occur on long-term use as well as any specific warning pertaining to long-term use of the drug are mentioned in this column of the drug profile wherever necessary.

Any changes in the patients' health must be reported to the doctor, for example, if the patient gets pregnant, it is important to ask her doctor if it is proper to continue the drug in pregnancy or change the drug. Similarly if one contracts a new disease/disorder, for which other drugs are prescribed, the doctor must know about it. The doctor must be informed, in case s/he does not know about the regular long-term drug you are using, when you consult him/her for another new disease/disorder. It is also advisable to carry a warning card mentioning that you are using a particular drug regularly along with you as it may prove useful in case of emergency, such as an accident.

Try to take the drug at the same time every day to avoid the chances of missing any dose. Certain long-term use drugs may require the patient to go to the doctor for regular check-ups, for example, blood-pressure measurement, blood count, certain blood tests, etc.

It is often thought that regular long-term use of certain drugs may result in reduced effectiveness of the drug or dependence of the patient on the drug. Now, this is true only for a few drugs and not for most of the other drugs. Besides, a drug if taken for few weeks may not cause such problems.

Annexure 1 is a brief discussion of some of the more commonly used drug groups.
Annexure 2 is about poisoning, including drug poisoning, and its treatment.

Guidelines for Safe and Effective Drug Use

Do Not

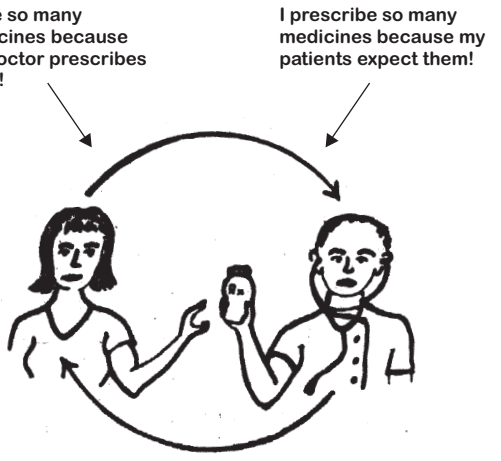
* Pressurise your doctor to prescribe unnecessary drugs.
* Take drugs on the advice of friends who have had similar symptoms.
* Offer anybody drugs prescribed for you.
* Change the dose or timing of any drug without the advice of your doctor.
* Continue a drug which is causing adverse reactions. Contact your doctor as soon as possible.
* Take any drug if you are pregnant or breast-feeding, unless prescribed by your doctor, who is aware of your condition.

Do

* Know the name and the correct spelling of the drug you are taking. It is advisable to know both the brand name and its generic name.
* Check the product label before purchase to ensure that the expiry date is valid at the time of consumption of the drug.
* Read the package labels and inserts of all drugs so as to familiarise yourself with the contents of the product.
* Follow dosage instructions correctly.
* Shake all liquid suspensions of drugs thoroughly to ensure equal distribution of the ingredients.
* Use a standarised measuring device for liquid

Do not

* Withhold from your doctor, information about your previous drug experiences. It is important that your doctor be informed about the beneficial and undesirable drug effects you had experienced in the past. Doctor, who is aware of your condition.
* Withhold from your doctor, information about your previous drug experiences. It is important that your doctor be informed about the beneficial and undesirable drug effects you had experienced in the past.
* Take drugs in the dark. Identify every dose of medicine carefully in adequate light to be certain you are taking the drug intended.
* Keep different medicines on the bedside table. You are likely to be confused and take the wrong one, even with the light on.
* Discontinue taking a prescribed drug abruptly without the doctor's advice.
* Take drugs which have expired.


I take so many medicines because my doctor prescribes them!
I prescribe so many medicines because my patients expect them!

THE VICIOUS CIRCLE THAT LEADS TO THE OVERUSE OF MEDICINE

Source: David Werner

Do

medications to be administered by mouth. The household teaspoon varies greatly in size.

* Follow your doctors's instructions on dietary and other treatment measures designed to augment the actions of the prescribed drugs. This makes it possible to achieve desired effects with smaller doses. A common example is to reduce salt intake during drug treatment for high blood pressure.
* Inform your doctor if you intend to take OTC drugs while on prescribed medication.
* Inform your surgeon, dentist, anaesthetist of all drugs you are taking or have been taking prior to any surgery.
* Inform your pathologist of all drugs you are taking prior to a diagnostic test.
* Keep a written record of all drugs (and vaccines) you have taken during your pregnancy and reasons for their use.
* Keep a written record of all of all drugs (and vaccines) to which you experienced allergic or adverse reactions.
* Inform your doctor if you are on a special diet, low-salt or low-sugar diet.
* Determine if you can drive a car, operate a machinery or engage in hazardous activity while on prescribed medication.
* Determine if alcoholic beverages can be taken while on prescribed medication.
* Determine the course of action if you miss a dose of the prescribed drug.
* Discard all outdated drugs. This will prevent used of drugs that have deteriorated with time.
* Store all drugs away from the reach of children to prevent accidental poisoning.
* Store all drugs away from heat, light, in airtight containers in a dry place.
* Keep all appointments and follow-up medical examination to determine the effects of drugs and the course of your illness.

Annexure

Some Common Drug Categories and How they Work

This appendix is a brief description of some of the more common drug categories one is likely to come across:

Analgesics/Painkillers
Antacids and Antiulcer Drugs
Antidepressants
Antiamoebics
Antianemics
Antibiotics
Antibacterials
Antimalarials
Antiemetics
Antifungals
Antitussives
Antihistaminics
Antihypertensives
Antituberculosis
Antivirals
Laxatives
Steroids

1. Analgesics (Painkillers)

Pain is an unpleasant symptom and not a disease. Pain suggests some disturbance in the body. It is hence necessary to correct this disturbance to cure the pain. A painkiller drug gives you only temporary relief from pain, e.g., the pain of toothache can be relieved by pain-killer but can only be cured by appropriate dental treatment.
It is therefore, important to determine the cause of pain in all cases. However this is not always very easy. Hence painkillers play a very important role in providing immediate relief to the patient till the cause is found and treated. Sometimes, when the underlying cause is irreversible, long-term analgesic treatment may be necessary.

TypesofAnalgesics

The main two types of analgesics are Narcotics and Non-Narcotics.

Narcotics are very strong analgesics. They are available only on doctor's prescription, since they are habit-forming and exert other harmful adverse effects too.

Non-Narcotic analgesics are less powerful and they include aspirin, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). They are OTC drugs and hence widely used. Whenever one uses OTC analgesics to treat pain, one must always consult the doctor if the pain persists for more than 48 hours after taking the drug.

While treating pain, treatment is first started with a non-narcotic. If that is not sufficient to relieve pain a strong narcotic may be used. Thus narcotic analgesics are used only to treat very severe or long lasting continuous pain like post-operative pain (pain after surgery) or pain in cancer, etc.

A doctor weighs the risk-benefit ratio of using a narcotic analgesic and decides to use it in a patient who, he feels, is miserable with a pain that would be more harmful than the side-effects of the narcotic drug. Sometimes elderly persons whose health is deteriorating day by day and who have very little chances of survival are given injections of narcotic analgesics so that they die peacefully (however, this is not legal in India as yet).

Headache

It is the most common type of pain that occurs in a majority of individuals. Over-the-counter analgesics are widely consumed for headaches. Hence we shall discuss 'headaches' briefly.

Headaches can be broken into 3 major categories:

1. **Tension or Muscle Contraction Headaches:** They are caused by busy, demanding schedules, worries and emotional upsets. The pain is usually constant, with a pressure like feeling primarily in the front but sometimes at the top and in the neck, and varying only in intensity throughout the attack. Dizziness and light-headedness may also occur.

2. **VascularH eadaches:** They are blood-related headaches and include migraine, cluster and toxic types of headache.

3. **Headachesduetophysicalandorganicconditions:** Migraine headaches last from several hours to several days with severe, throbbing pain on one side of the head accompanied by nausea, vomiting, sensitivity to light and limited ability to function normally. Spots and flashes, speech difficulties and loss of feeling may be warning signs of an attack.

Cluster headaches occur in clusters, that is, one to three headaches a day, each lasting from ten minutes to few hours. The pain is similar to migraine related pain and the symptoms include flushing of the forehead, tearing of the eyes and nasal congestion.

Toxicheadaches occur due to various reasons, some of which are listed below:

- Chemical from food
- Fumes from industrial plants or engine exhaust
- Substances in food such as cheese and bananas as well as fermented products such as red wine
- Nitrite preservatives commonly used in processed meat and the flavour enhancer monosodium glutamate (MSG) in prepared food.
- Alcohol, cigarettes
- Allergies to various pollens, moulds, or other substances are also triggering factors when headaches are seasonal.
- Changes in attitude and weather
- Hunger (for long periods)

Headachesduetophysical(organic)diseasesorconditionsmayresultfrom

- Fever associated with an infection
- Problems of the ears
- Sinus
- Teeth
- Facial nerves

- Injuries
- Eye problems
- Anaemia
- More serious health problems (rarely)

Whenshouldyouconsultthedoctor?

A doctor should be consulted when:

- Headache continues for 48 hours after taking the recommended dose of painkillers, or returns back
- Headaches occur frequently
- Headaches interrupt sleep or impair one's ability to function normally
- Headaches are accompanied by fever, vomiting, weakness, dizziness, numbness, loss in balance or any unusual sensations.

RecognisingHeadache-CausingSituations

In case of frequent headaches, it is advisable to maintain a record of every headache you suffer from. The points to be noted are date, day and place of occurrence, time of onset, duration, warning signs before occurrence, type and severity of pain, other symptoms, mood of patient before onset, food/medicines etc., taken before occurrence, activities done before occurrence and source of relief.

Keeping such a record will help the doctor find the correct type/cause of headache and treat it accordingly.

ManagementofHeadaches

The more well-known analgesics, namely paracetamol, aspirin and ibuprofen, are usually used to treat occasional and/or mild headaches. Severe headaches like migraines and cluster need other specific drugs (which the doctor prescribes). Tension or Muscle Contraction headaches can be managed by understanding the cause of pain and using self relaxation which can be done in any of the following ways:

- Lying down in a dark room
- Taking a nap
- Listening to music
- Taking a hot water bath
- Yoga and meditation
- Exercise

TreatmentofPain

The most widely used analgesics for mild-pain are aspirin and paracetamol. Aspirin is the analgesic of choice for headache, muscular pain, bone and joints pain and pain due to menstruation. It also has helpful anti-inflammatory (reduces swelling) and antipyretic (reduces fever) properties, which are exhibited at somewhat higher doses. Its drawbacks are that it causes stomach irritation (which can be minimized if taken after food) and hence it is not used to treat abdominal pain or pain associated with nausea and vomiting. It is also not to be used in children below 12 years of age.

Paracetamol is similar in efficacy to aspirin but has no anti-inflammatory activity. However, it is less irritant to the stomach as compared to aspirin. It can be used in children. Its overdose is dangerous as it causes severe liver damage.

Non-Steroidal Anti-inflammatory analgesics (NSAIDs) are used to treat patients with chronic diseases accompanied by pain and inflammation, for example, arthritis, secondary bone tumors, etc. They include drugs like ibuprofen, naproxen, piroxicam, diclofenac, indomethacin, diflunisal, etc. They differ in efficacy and side-effects. Ibuprofen is widely used. It has fewer side-effects than other NSAIDs but its anti-inflammatory properties are weaker. Whereas the side-effects of indomethacin are very many.

NSAIDs must be used with caution in the elderly, pregnant, asthmatic, allergic, cardiac and renal and/or hepatic impairment patient. They like aspirin, cause stomach irritation and must be avoided in ulcer patients.

Narcoticanalgesics, also known opioid analgesics, are the most powerful analgesics. However, they have harmful side-effects and habit forming potential and hence not used for mild pain. They are used to treat pain arising from surgery, serious injury and disease. They are valuable for alleviating severe pain during terminal illnesses, e.g., cancer. Morphine is the most well known narcotic analgesic. Others are diamorphine (heroin), pethidine, phenazocine, etc. The use of these powerful narcotic analgesics is strictly controlled as they produce euphoria, which can lead to abuse and addiction. But when they are used under medical supervision for treatment of severe pain for a short period of time, the risk of addiction is very little.

There are less powerful drugs in this group which are used to relieve mild to moderate pain, e.g., codeine (which though effective is too constipating for long-term use) and dextropropoxyphene (a mild analgesic and less potent than codeine).

CombinationAnalgesics

Although there are many combination analgesic products (like Brufen, a combination of paracetamol and ibuprofen) available in the market, there is little evidence that such products are more effective than the single drug. Besides they combine the side-effects of both drugs. Hence it is advisable to use a single analgesic which is effective rather than using combination products.

Source: EDM Issue No 30, 2001

2. Antacids and Antiulcer Drugs

Acidity

The digestive juice in the stomach contains hydrochloric acid and an enzyme 'pepsin', which help in digestion of food. The wall of the stomach is protected from the action of the acid, by a lining called the 'mucus lining'.

When the mucus lining is damaged or when excessive acid production eats up the mucus lining, the stomach acid comes directly in contact with the stomach wall resulting in pain and inflammation. This disorder is known as Acidity. The symptoms of acidity include burning sensation in the stomach and/or chest regions, pain, indigestion, discomfort. Acidity may result from overeating, use of coffee and alcohol, smoking, anxiety, ingestion of certain foods/drugs.

PepticUlcer

When very large amount of acids are produced, the mucus lining is excessively damaged. This can lead to erosion of the underlying tissue resulting in 'ulcer' or 'peptic ulcer' ('peptic' word arising from the name 'pepsin', the stomach enzyme). The symptoms of peptic ulcer include pain, vomiting and loss of appetite. Peptic ulcer can occur in the oesophagus, stomach or duodenum (first portion of the intestine), the duodenum being the most common site of occurrence.

Causes

The exact cause of ulcer is not fully understood. However one of the causes appears to be hereditary. Those individuals who produce excessive stomach acids are prone to ulcers. Others who have normal acid production may develop ulcer because the protective mucus lining is defective or inadequate. Other factors which can increase the incidence of ulcer are:

- Physical stress (burns, trauma, surgery)
- Irregular eating habits
- Anxiety, tension
- Use of certain drugs and foods
- Overuse of alcohol
- Overuse of coffee
- Heavy smoking

Certain drugs in use lead to excess acid production and on overuse result in ulceration.

They include:

- Alcohol
- Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs)
- Aminophylline
- Cortisone like steroids
- Phenylbutazone

Treatment

A) Antiacidity

They are used in acidity when simple remedies such as change in diet or a glass of milk fail to relieve the symptoms.

Antacids combine with the stomach acid to reduce the acidity of the digestive juices. This helps to prevent pain and inflammation.

Antacids are thus useful in the treatment of acidity. They are also used in the treatment of Peptic Ulcer as they relieve the pain (within a few minutes) and promote the healing of ulcer. However, they are not as effective as other antiulcer drugs.

TypesofAntacids

The duration of action and speed of action of antacids varies as the type of antacids varies.

1. Aluminum Compounds: They have prolonged action and are widely used. They can cause constipation and are hence combined with magnesium compounds, namely magnesium hydroxide to counteract that effect.
2. Magnesium compounds: Magnesium hydroxides is widely used. It has prolonged action. It can cause diarrhoea. It is usually combined with aluminium Compounds. It should be used cautiously in patients with kidney problems.
3. Sodium bicarbonate: It acts quickly but has short duration of action. It produces gas causing bloating in the stomach and belching. It should be avoided in heart and kidney patients.
4. Combined preparations: Antacids are often combined with alginates and antifoaming agents, e.g., dimethicone. These additives have no primary benefit and just add up to the cost of the product.

Precautions

- Do not take antacids on a regular basis without doctor's advice as it may suppress symptoms of some serious disease like stomach cancer.
- Antacids interfere with the absorption of many drugs. If you are taking other drugs, check with your doctor before taking an antacid.

B)AntiulcerDrugs

They are prescribed both to relieve the symptoms and to heal the ulcer.

There is no drug to cure a tendency to ulcer formation. Hence courses of antiulcer drugs are repeated regularly (especially for duodenal ulcers). Surgery is needed only for complication such as uncontrolled bleeding, obstruction, and perforation.

TypesofAntiulcerDrugs

1. H_2blockers: e.g., cimetidine, ranitidine, famotidine.

A chemical called 'histamine' which when released by certain cells in the body produces a variety of effects, one of them being acid production in the stomach. The acid producing cells in the stomach has H_2 (Histamine-2) receptors. The histamine binds with these receptors and triggers acid secretion. The H_2 blocker drugs bind with the H_2 receptors and thus prevent histamine from binding with them. This leads to reduction in acid production and ulcer healing.

2. Bismuth and Sucralfate: They form a coating over the ulcer, protecting it from the action of stomach acid and allowing it to heal.
3. Tranquilizers and Sedatives: May be used with antiulcer drugs to reduce anxiety and tension.

Precautions

Cimetidine and ranitidine are not prescribed for a period of more than 6 months. Cimetidine should be used cautiously in the elderly.

Sucralfate is prescribed for up to 12 weeks while bismuth is prescribed for courses of four weeks. It is important to drink plenty of water with bismuth. Sucralfate should be taken on empty stomach.

3. Antiamoebic Drugs

Amoebiasis is a common infectious disease caused by the organism *Entamoeba histolytica*.

Most persons who get infected with E. hisolytica do not get the disease. The disease, which occurs in about 10% of infected persons mainly, involves the large intestine, but other organs of the body like the liver, lungs and brain may also get involved. The infection is frequently chronic, being present in the body for many months or years.

The organism *Entamoeba histolytica* is found in two forms:

1. The active form (known as trophozoite) is found in the large intestine and in the infected tissues of the body.

2. The inactive or dormant form (known as cysts), which are found in the intestine and excreted in the stool.

The disease is spread by the cysts, which contaminate water and food in situations where there is poor environmental sanitation. This process is assisted by poor hygiene and insects like flies. In some areas, vegetables grown in fields irrigated with water contaminated by sewage can spread infection. The cysts, which are ingested by an uninfected person, pass into their intestines where the cyst wall breaks open and the active forms of the parasite are released, which then enter the walls of the large intestine.

The organism may sometime spread to the liver, lung, brain, skin and other organs through the bloodstream.

Symptoms of amoebiasis vary according to the part of the body involved. Intestinal amoebiasis is the most common form and this presents as acute amoebic dysentery with blood and mucus in the stools, pain in the abdomen and a painful, recurrent urge to pass stools (known as tenesmus). The disease may evolve into a chronic phase with loss of appetite (anorexia), pain in the abdomen and intermittent constipation or diarrhoea. However, many persons who pass the cysts in their stools may not have any symptoms at all, and function as "carriers" of the diseases.

Sometimes the organism travels to other organs of the body through the blood stream, such as the liver, lungs and brain. These forms of amoebiasis are known as extra-intestinal amoebiasis. The symptoms and signs are related to the organs involved.

The prevention and control of amoebiasis involves improvement of sanitation - the provision of safe drinking water and the safe disposal of excreta. Food hygiene, which involves the protection of food and drink from faecal contamination, is also important - the disinfection of uncooked fruits and vegetables should receive particular attention. Those persons handling food in eating establishments should practice a high level of personal hygiene, including frequent handwashing with soap and water.

TypesofAntiamoebicDrugs

The drugs used to treat amoebiasis are mainly of two types:

Drugs used only in intestinal amoebiasis - eg., diloxanide, tetracycline, iodochlorhydroxyquin, diiodohydroxyquin.

Drugs used both in intestinal and extra-intestinal amoebiasis- eg. emetine, metronidazole, tinidazole, secnidazole.

ActionsofAntiamoebicDrugs

The different antiamoebic drugs act against E.histolytica in different ways - some interfere with its metabolism, others act directly on the nucleus of the parasite and some alter the growth of bacteria in the intestine, which affect the growth of the parasite.

Side-EffectsofAntiamoebicDrugs

Local reactions - some drugs given by injection may cause swelling and pain at the site of the injection.

Allergic reactions: generalized itching, skin rashes, flushing, chills, fever.

General reactions - a sensation of vomiting (nausea), vomiting, diarrhoea, giddiness, a metallic taste in the mouth, pain in the abdomen.

Nervous system (neurological) side-effects: headache, weakness, unsteadiness in standing and walking (ataxia), dizziness (vertigo), epileptic convulsions, inflammation of nerves (neuritis).

Heart and blood vessels: increased heart rate (tachycardia), chest pain, decrease in blood pressure (hypotension), inflammation of the heart muscle (myocarditis) and its covering (pericarditis).

Eye: inflammation of the nerve supplying the eye (optic nerve), leading to blindness - this has been observed in Japan mainly.

Precautions

1. Alcohol should be avoided when taking these drugs as it causes unpleasant reactions such as sweating, vomiting, flushing and a fall of blood pressure.
2. Pregnancy - these drugs should be avoided during pregnancy, especially during the first three months.

They should also be avoided by breast-feeding mothers.

3. Kidney or heart disease - some antiamoebic drugs should be avoided in persons having these problems.
4. Children - some antiamoebic drugs should be avoided.

UseofAntiamoebicDrugs

Amoebiasis is an extremely common disease and is difficult to treat, as it tends to become chronic. Re-infection through the ingestion of infected food or water is very common. The antiamoebic drugs often fail to completely eradicate the parasite in the body.

Some of the antiamoebic drugs only act n intestinal amoebiasis, while others act in intestinal as well as extra-intestinal amoebiasis. The choice of drug to be used in a particular patient thus depends on the type of amoebiasis, which the patient has.

Certain persons handling food in hotels, restaurants and other food establishments are found to be passing the cysts of *E. histolytica* in their stools. It is necessary to treat these patients so that they do not spread the infection and so pose a risk to others. Some antiamoebic drugs act on the cysts and can eradicate them from the intestines of such infected person.

Hence antiamoebic drugs are used in the following situations:

1. Intestinal amoebiasis - amoebic dysentery.
2. Extra-intestinal amoebiasis - amoebic hepatitis, amoebic liver abscess, lung abscess, brain abscess.
3. Those passing cysts but otherwise without sypmtoms.

MisuseofAntiamoebicDrugs

Anti-amoebic drugs are often misused. One very common example of misuse is the treatment of all types of diarrhoea with these drugs, even those types that are not caused by *E. Histolytica.*

Source: EDM Issue No 30, 2001

4. Antianemics

Anemia is caused by the deficiency of 'Haemoglobin', the red colour pigment in the blood, which carries oxygen to various parts of the body. The blood cells which contain haemoglobin are called the red blood cells (RBCs). The formation of the RBCs is affected if a person is suffering from deficiency of proteins, iron, folic acid or Vitamin B-12. This leads to deficiency of haemoglobin in the blood resulting in anemia.

The commonest cause of anemia is the deficiency of iron (with or without folic acid) which arises due to various reasons such as:

- Excessive blood loss during menstruation in some women
- Repeated pregnancies
- Bleeding piles
- Blood loss due to ulcers in the gut
- Hookworm infestation (since hookworms suck blood from the intestines).
- Blood loss due to chronic diarrhoea
- Blood loss due to injury or accident
- Inadequate diet.

SymptomsofAnemia

- Tiredness and weakness
- Pale tongue and nails
- Shortness of breath on usual exercise/work
- Palpitations
- Irritability
- General pallor

GeneralGuidelines

It is far better to prevent anemia by using iron supplements in a patient who is likely to develop anemia rather that treating it later when developed. Supplements are therefore given:

- throughout pregnancy
- to patients with excessive blood loss (because of causes mentioned above)
- to premature babies, twins and infants delivered by caesarian section

Patients of anemia should be advised to eat foods which are good source of iron such as green leafy vegetables, bajra, ragi, beans and pears and jaggery. Non-vegetarians can eat meat, fish and chicken which are also rich in iron content.

Besides iron-deficiency anemia, there are other types of anemia also. Iron supplements can prove harmful if given alone to patients with anemias other than those due to iron deficiency. Thus different types of anemia require different types of drug treatment.

5. Antibiotics

Penicillin, the first antibiotic, was discovered in 1941. Since then many new and different classes of antibiotics have been introduced. Each antibiotic is a different chemical entity and is effective against a broad or specific spectrum of bacteria, used in the treatment of specific organisms. Antibiotics and antibacterials are not effective against viruses.

Bacteria are present all around us - in the air we breathe, in the mucous membranes of the mouth and nose, on the skin, in the intestines. Our natural immunity protects us from them. But when our immunity breaks down, or when bacteria already present migrate to a vulnerable new site, or when harmful bacteria not usually present invade the body, infectious disease sets in. Bacteria multiply rapidly, destroying tissue, releasing toxins and, in some cases, threatening to spread via the bloodstream to such vital organs as the heart, brain, lungs and kidneys. The symptoms of infectious disease, although they almost always include fever, vary widely, depending on part of the body infected and the type of bacteria.

The exact kind of bacteria infecting a person can only be confirmed by tests of the person's blood, sputum, urine, stool or pus. These can take up to 24 hours or more. In the absence of such tests, the doctor usually makes an educated guess and may prescribe a broad-spectrum antibiotic that is an antibiotic that works against a wide range of bacteria.

With more exact information from the laboratory tests confirming the nature of the

bacteria, the doctor may then switch to an antibiotic that is the recommended treatment for the identified bacteria. Sometimes more than one antibiotic is prescribed to be sure of eliminating all strains of bacteria.

Antibiotics come in the form of tablets, capsules, liquids, dry syrups, or injectables. The last is normally used in critical cases. There are also antibiotic that are topical preparations used for skin, eye and ear infections.

Antibiotics either kill organisms directly (bactericidal), or enabling the body's natural defences to overcome the remaining infection.

There are two main mechanisms of action: penicillins and cephalosporins destroy bacteria by preventing them from making normal cell walls; most other antibiotics act inside the bacteria, interfering with the chemical activities essential to their life cycle.

While antibiotics act against infections, they may not relieve symptoms directly; in such cases additional medication such as painkillers to relieve pain and fever may be prescribed until the antibiotics start to take effect.

As with all medicines, the complete course of medication must be prescribed and complied with by the patient even if all symptoms seem to have disappeared or the patient "feels better". Failure to complete the course can lead to the infection again and worse result in the long-term in resistance to the antibiotic.

The other reason for increase in antibiotic resistance is wrong prescription or using a stronger second or third generation antibiotic (like norflaxacin) when a first-generation (like amoxycillin or doxycycline) would do. Also, antibiotics, for instance, may lower the natural immunity of the body to certain kinds of yeast which

in turn mat lead to fungal infections in the mouth, throat and vagina. An antifungal drug would need to be prescribed then.

Nausea and diarrhoea are rather common side-effects of antibiotics. Do not normally stop the antibiotic in such cases. The most common risk, particularly with penicillins and cephalosporins, is allergic reactions that cause rashes and sometimes swelling of the face and throat. If this happens the drug should be stopped and immediate medical advice sought. Some people are sensitive to particular types of antibiotics, say the penicillins, and this can lead to serious adverse reactions.

A rarer, but more serious and fatal, disorder occurring especially with the lincosamide class of antibiotics is a disorder called pseudomembranous colitis, in which bacteria that are resistant to the antibiotic multiply in the bowel, causing violent, bloody diarrhoea.

Antibiotics must be used with caution.

CommonAntibioticsDrugs

Penicillins
Amoxycillin
Ampicillin
Benzylpenicillin
Cloxacillin
Phenoxymethylpenicillin
Procaine Penicillin

Cephalosphorins
Cefaclor
Cefoxitin
Cephalexin
Cephazolin
Cephatoxime
Cephtriaxone

Aminoglycosides
Gentamicin
Neomycin
Netilmicin
Streptomycin
Tobramycin
Amikacin

Tetracyclines
Doxycycline
Oxytetracycline
Tetracycline

Macrolides
Erythromycin
Clarithromycin
Azithromycin
Roxithromycin

Lincosamides
Clindamycin
Lincomycin

Quinolones
Ciproflaxacin
Norflaxacin

Other Antibiotics
Chloramphenicol

Germs are smart...
They develop resistance to the medicine we take and are tougher to kill.
...we are smarter!
With our doctor's help we are able to take the appropriate antibiotic exactly as required to stop even the toughest of bacterial infections.

This APUA patient leaflet clearly spells out the dangers of antibiotic resistance.

6. Antibacterials

Antibacterials are similar to antibiotics but with a difference: originally antibiotics were derived from moulds and fungi, whereas antibacterials were developed from chemicals. Early antibacterials like the sulpha-drugs were derived industrial dyes that was metabolized by the body into sulphanilamide, the active antibacterial ingredient. Sulpha drugs, introduced in the 1930s, have proved to be effective against many bacterial infections.

Sulphonamides followed the original sulpha drugs. Bacterial resistance to sulpha drugs, like that of resistance to antibiotics, have resulted in doctors switching over to antibiotics that are more effective and safe. But the days of the sulphonamide antibacterials are not yet over.

Sulphonamides reach high concentrations in the urine. They are therefore useful in treating infections of the urinary tract. They are also used for chlamydia, pneumonia and for some middle ear infections; sulphacetamide is often included in topical preparations for skin, eye and other ear infections. Sulphamethoxazole, in combination with trimethoprim, often in a single large dose (also known as co-trimoxazole), is used for bladder infections, certain types of bronchitis and some gastrointestinal infections.

There are of course a range of antibacterials that are not sulphonamides: those used against leprosy, TB and malaria; those used against protozoal infections (like metronidazole, diloxanide furoate). There are others, also known as antimicrobials, include metronidazole, used for a variety of genital infections, and some serious infections in the abdomen, pelvic region, the heart and central nervous system. Nalidixic acid and nitrofurantoin are effective as antiseptics for the urinary tract, and are used to cure or prevent recurrent infections.

Antibacterials work by preventing the growth and multiplication of the organisms, somewhat similar to antibiotics. Antibacterials may take several days to wipe out the bacteria. During this time additional medication to relieve pain and fever is usually advised. Sulphonamides in particular can cause loss of appetite, rash, nausea and drowsiness.

Risks and special precautions of antibacterials include allergic reactions, rashes and fever. The doctor should be consulted in case a change of antibacterial is required. Serious, but rare risks, with some sulphonamides include formation of crystals in the kidneys, a risk that can be reduced by drinking adequate amounts of fluid during prolonged treatment. Sulphonamides may occasionally damage the liver; they are not usually prescribed for people with liver problems. Damage to bone marrow is another possibility, leading to lowered production of white blood cells and increased chances of infection. Doctors therefore try avoiding use of sulphonamides for long periods. It is advisable to monitor the liver and blood content, during long-term treatment that may be absolutely necessary.

SomeCommonAntibacterials

Sulphonamides	*Other Antibacterials*	*Urinary antiseptics*	*Nitroimidazoles*
Co-trimoxazole	Dapsone	Nalidixic acid	Metronidazole
Sulphacetamide	Trimethoprim	Nitrofurantoin	Tinidazole
Amphotericin	Ketoconazole		
	Fluconazole		
	Flucytosine		

7. Anti-Depressant Drugs

Depression is a mood of sustained unhappiness or sadness. It is a common psychiatric problem present in the general population and is often unrecognised and underdiagnosed. It is also a potentially serious problem that can disrupt normal life and drive the affected person to attempt suicide.

Depression is more common in the elderly and the highest incidence occurs in the sixth and seventh decades of life, and in women slightly earlier than men.

There are two major types of depression:

1. Unipolar depression - in which the depression is either reactive or endogenous. Reactive depression occurs after a particular event such as death in the family, sudden misfortune, accidents etc. Though emotional feelings are intense, the individual responds to support from friends and relatives who can share problems and discuss solutions.

   Endogenous depression usually occurs in the middle or later years of life, and more commonly in women than in men. There is a general slowing down of body, mind and speech - the individual withdraws from usual activities. Other symptoms include feelings of guilt, inferiority and anxiety. The individual may also complain of early morning awakening, occasional nightmares, loss of appetite, loss of weight and loss of libido.

2. Bipolar depression (manic-depressive psychosis or MDP) - here the depression is associated with mania - each condition occurring alternately.

The causes of depression are not certain. In certain types of depression (eg., reactive depression) there may be a precipitating factors such as those mentioned above. However, in other types of depression, there may be no obvious cause.

Depression has been associated with a depletion of certain substances in the brain which are known as neurotransmitters. The neurotransmitters include 5-hydroxytryptamine (5HT) or seratonin, and monoamines.

Effective anti-depressant drugs are available now which can relieve most of the symptoms and complaints and enable the affected individual to lead as normal a life as may be possible. This treatment in most cases can be given at home and admission to hospital is not necessary.

TypesofAnti-DepressantDrugs

There are four main groups of anti-depressant drugs:

1. Tri-cyclic anti-depressants - these are the most commonly used drugs and include imipramine, disimipramine, amitryptiline, nortryptiline, clomipramine, etc.
2. Monoamine oxidase inhibitors (MAOI), eg., isocarboxazid, iproniazid, tranylcypromine.
3. Selective seratonin re-uptake inhibitors (SSRI), eg., fluoxetine, paroxetine, sertraline.
4. Others, eg., carbamazepine, lithium.

ActionofAnti-DepressantDrugs

Depression is associated with the depletion or decreased effectiveness of certain substances known as neuro-transmitters in the nerve endings in the brain. These substances are acted upon by enzymes. Anti-depressant drugs act by inhibiting the action of these enzymes on the neuro-transmitters and so prevent their depletion.

Anti-depressant drugs take about two to three weeks to start their action. When this happens, the mood of depressed individuals is improved. Such persons feel more active and less lethargic. Suicidal thoughts are markedly reduced. Some drugs also reduce the anxiety associated with depression.

Side-EffectsofAnti-DepressantDrugs

Anti-depressant drugs have a wide range of side-effects, and it is important to keep these in mind when they are being used.

1. Allergic reactions - severe itching, skin rashes, sensitivity to light (photosensitivity).
2. Nervous system - Fatigue, headache, lethargy and drowsiness may occur, and some anti-depressant drugs are highly sedative. Other drugs may cause inability to sleep (insomnia), anxiety and decrease in libido. Other side-effects include twitching, tremors, inability to walk, convulsions, high body temperature (hyperthermia).
3. Heart and blood vessels - increase in the heart rate (tachycardia), disturbances in heart rhythm, decrease in blood pressure in the standing or erect posture, sudden and sustained high blood pressure if certain foodstuffs are taken at the same time (eg., cheese, beans, buttermilk, curds, chocolate and soyabeans).
4. Behavioural problems - excitement, anxiety, excessive activity or elated mood (mania), hallucinations.
5. Dryness of mouth, difficulty in urination, constipation, high body temperature, difficulty in vision - these are all known as anti-muscarinic effects.
6. Others - jaundice, swelling of feet, white blood cell abnormalities.

Precautions

Anti-depressant drugs interact with many other drugs and foodstuffs and these interactions should be kept in mind when using them. This interaction results in one of the following:-

a. Enhancement, prolongation or decrease of the action of the drug given along with the anti-depressant drug.

b. Enhancement of the action of the anti-depressant drug.

c. Increase in side-effects of anti-depressant drug eg. sudden and sustained increase in blood pressure resulting in other side-effects.

MAOI anti-depressant drugs interact with the tricyclic and SSRI drugs.

OtherPrecautions

- Elderly: some anti-depressant drugs should be used cautiously in the elderly as they give rise to dizziness, constipation, decrease of blood pressure in the erect posture.
- Persons requiring to be mentally alert (eg., those operating machinery or driving) should also be careful

as some anti-depressants are sedative or cause dizziness.

TreatmentofDepression

Depression is a common psychiatric problem found in the general population. To minimise the disruption of the social life of the affected individual, it is essential that the condition is diagnosed as early as possible and treatment started immediately. Anti-depressant drugs are very effective and can bring about improvement in a large number of cases.

In the treatment of depression, it may be necessary to search for other factors that contribute to the illness and attempt to reduce their impact. The choice of the anti-depressant drug used depends on the age of the patient, presence of associated symptoms (like anxiety or excitement), need for sedatives and the side-effects which are to be avoided.

Anti-depressant drugs require a minimum of two to three weeks to start acting, and good recovery in most cases occurs within four to eight weeks. The treatment should be continued for eight to twelve months atleast. However, some cases may need treatment to be given life long, as there may be a risk of relapse if the treatment is stopped. Tolerance develops to some of the side-effects, so the drugs should not be stopped abruptly. The side-effects of anti-depressant drugs are numerous - however they do not always occur. If they appear, it is usually during the first few days of treatment. Though drug treatment is effective, affected individuals need constant support from their family, relatives and friends.

- Depression is a common problem in the general population.
- It is potentially serious - may lead to suicide.
- Effective drugs are available that relieve many of the symptoms and complaints.
- Treatment at home is possible in most cases.
- Side-effects and drug interactions should be kept in mind while using anti-depressant drugs.
- Affected persons need support from family, relatives and friends.

Many patients are led to believe, by their physicians and by advertising, that antidepressant drugs will act on the biological cause of their depressed state by rectifying a "chemical imbalance" … On the contrary, our analysis indicates that there are no specific antidepressant drugs, that most of the short-term effects of antidepressants are shared by many other drugs, and that long-term drug treatment with antidepressants or any other drugs has not been shown to lead to long-term elevation of mood. We suggest that the term "antidepressant" should be abandoned. We have proposed an alternative drug-centred model of drug action that is consistent with a demedicalised approach to depression.

Quoted in: Moncrieff J, Cohen D (2006) Do Antidepressants Cure or Create Abnormal Brain States? *PLoS Med* 3(7): e240

8. Antiemetics

Antiemetics are drugs used to suppress vomiting and nausea. Vomiting (emesis) is a process by which the body throws out harmful substances or a symptom of some disease/disorder.
Vomiting can result due to various causes and the treatment varies with the cause.

The common causes of vomiting include:

1. Ingestion of nauseating or irritating material including spoilt food.
2. Infection due to some disease/disorders of the digestive tract.
3. High fever
4. Pregnancy
5. Motion sickness
6. Vertigo (reeling sensation)
7. Migraine
8. Serious illnesses such as painful fracture, heart attack, stomach pain, brain disease, head injury, closed stomach injuries with internal organ damage, stomach ulcer, etc.
9. Side-effect of a drug/radiation therapy/general anaesthesia.

Treatment

When the vomiting is due to ingestion of spoilt food or irritating substances, it helps to throw out the irritating material and hence is beneficial. However, excessive vomiting causes loss of salt and water and exhausts the patient. Hence the patient should take sips of cold water and dehydration fluid. Food be avoided as far as possible. Such type of vomiting is self-limiting.

Anti-emetics are usually taken to prevent motion sickness (dimenhydrinate can be used), to suppress nausea due to drug treatment (domperidone, phenothiazine can be used), to suppress nausea in vertigo and to relieve severe vomiting in pregnancy (phenothiazine can be used).

An antiemetic should not be taken for longer than a couple of days without consulting the doctor. A doctor usually diagnoses the cause of vomiting because vomiting can require other treatments (e.g., vomiting due to infection may require surgery), instead of antiemetic treatment. Suppressing vomiting in such cases may delay treatment and recovery.

One must always consult the doctor in the following cases of vomiting.

- If the vomiting is accompanied by acute abdominal pain, severe chest pain, severe headache, high fever, convulsions or dehydration.
- If the vomit contains blood.
- If the vomit is dark coloured and foul smelling
- If the vomit is not controlled within 24 hours and the patient looks ill.
- Persistent vomiting in pregnant women.
- All patients with a history of repeated attacks of vomiting of long duration.

Remember

- A patient who is vomiting should not eat solid food. He/she must take sips of ice-cold water, cold weak tea, lime juice or dehydration fluid/ORS especially if diarrhoea is also present. Addition of a pinch of ginger powder would help.
- Take a sample of vomit, if available for examination by the doctor when you go for consultation.
- A pregnant lady suffering from vomiting should not take any antiemetic without consulting her gynaecologist (some antiemetics can be harmful to the unborn baby).
- If decreased urine output is noticed, increase the fluid intake.

Howdoantiemeticswork?

Vomiting occurs when the vomiting centre in the brain is triggered by signals which arise from the stomach, the inner ear or in other parts of the brain.

Antiemetic drugs may act at one or more of these places in the body, and prevent vomiting. They may also promote the normal emptying of the stomach contents into the intestine thus preventing the expulsion of the stomach contents.

Precautions

Antiemetics like phenothiazines and metoclopramide should not be taken by patients who suffer from movement disorders such as 'Parkinsonism', as they can aggravate such conditions.

Antiemetics which are also antiallergics, e.g., promethazine, diphenhydramine, etc., produce many other actions such as dry mouth, blurred vision, difficulty in passing urine and drowsiness. It is advisable not to drive while taking such antiemetics.

CombinationProducts

Combination products containing (a) more than one antiemetic or (b) an antiemetic with analgesic have got no special beneficial effects over a single product containing only one antiemetic.

Source: EDM Issue No 30, 2001

9. Antifungal Drugs

Fungal infections of humans are caused by different types of fungi. They occur both by themselves and in association with other conditions such as diabetes and certain cancers. They are also found in conditions where the immunity is decreased (such as in HIV/AIDS) and in persons taking antibiotics and steroids.

Fungal infections are spread by inhalation of spores and by contact with the skin of an infected person. There are three kinds of such infections:

1. Generalised (systemic) fungal infections such as Candida, histoplasmosis (affecting the lungs), aspergillosis, cryptococcosis. These infections are relatively uncommon.
2. Deep skin (subcutaneous) fungal infections such as sporotrichosis, zygomycosis, mycetoma (also known as Madura foot) and Pneumocystis carinii infection (in adults usually associated with HIV/AIDS).
3. Superficial fungal infections of the skin, hair, and nails such as ringworm, dandruff - these are common in warm and humid climates. They are especially frequent in individuals with poor personal hygiene.

TypesofAntifungalDrugs

Antifungal drugs are of two major groups:

1. Those used for generalised (systemic) infections - they are available in the form of tablets or injections. They belong to different categories, as follows:

a. Antibiotics, eg., griseofulvin, amphotericin.

b. Synthetic drugs, eg., ketoconazole, clotrimazole and fluconazole.

c. Others, eg., flucystocine, terbinafine.

2. Those used for local (superficial) infections - these are available as creams, ointments and lotions:

a. Antibiotics, eg., nystatin.

b. Synthetic drugs, eg., miconazole, clotrimazole, ketoconazole.

c. Others, eg., benzoic acid, salicylic acid, selenium sulphide, ichthammol.

Most superficial fungal infections are treated with local antifungal drugs. Certain chronic, widespread infections may require treatment with drugs for generalised (systemic) infections.

ActionofAntifungalDrugs

The antifungal drugs inhibit the growth of fungi (fungistatic action) through different mechanisms. Some of them kill the fungal organisms (fungicidal action). Some also act on bacteria.

Side-EffectsofAntifungalDrugs

The side-effects of antifungal drugs are mainly seen with the drugs given by mouth (orally) or by injection. The drugs used for local treatment seldom give rise to side-effects.

The following are the main side-effects of antifungal drugs:

- General problems like headache, pain in the stomach, sensation of vomiting (nausea), vomiting and diarrhoea.

- Allergic reactions - itching, skin rashes, fever, sensitivity of skin to light (photosensitivity).
- Damage to the liver and / or the kidney.
- Blood disorders - abnormalities of the blood cells, anaemia.
- Disturbances of the nervous system such as inflammation of nerves (neuritis), dizziness (vertigo), feeling of laziness (lethargy), tiredness, blurred vision, convulsions.
- Decreased blood pressure (hypotension), heart failure and other problems with the heart and blood vessels.
- Other miscellaneous side-effects - enlargement of the breast in males (gynaecomastia).

UsesofAntifungalDrugs

To treat superficial fungal infections of the skin:

Ringworm of the skin, nails, scalp, beard, hands, feet and groin - here the locally acting drugs work well in most cases. In some persons with widespread involvement antifungal drugs taken by mouth are more effective and convenient.

Dandruff and seborrhoeic dermatitis - these conditions are also treated with locally acting drugs.

To treat generalised (systemic) fungal infections - in these conditions antifungal drugs are given by mouth or by injection for several days or weeks.

Precautions

Antifungal drugs used to treat generalised (systemic) fungal infections need to be taken strictly under medical supervision for several days or weeks. These drugs should be used cautiously in patients with liver diseases, and in elderly patients. Antifungal drugs used to treat local and superficial infections need to be applied to the affected areas once or twice a day for several days or weeks. To ensure a complete cure, treatment should be continued for atleast two weeks after all signs of the condition disappear. Certain fungal infections of the nails require continuous treatment for 12 - 18 months. Some antifungal drugs (eg. griseofulvin) interact with other drugs such as anti-convulsants, anti-coagulants, anti-diabetics and alcohol. Many antifungal drugs should be avoided during pregnancy and in breast feeding mothers.

10. Antihistaminic Drugs

This is a group of drugs used mainly in allergic conditions, and also to prevent nausea, vomiting and symptoms of travel sickness, dizziness (vertigo) and for more complex medical conditions. They counter the effect of histamine in the body.

Histamine is a substance found naturally in different parts of the body in cells of the blood and tissues, as well as in body fluids. Certain acute conditions like allergic reactions, injury by cold, heat and chemicals cause a sudden large release of histamine. When released histamine causes many effects on organs of the body, some of which are:

- Enlargement (dilation) of blood vessels causing a fall of blood pressure and symptoms like headache and flushing (feeling of warmth in one part of the body).
- Swelling of parts of the body (edema), along with itching and pain.
- Decrease in size (constriction) of the respiratory passages (bronchi) leading to an asthma-like condition

TypesofAntihistaminics

Older antihistaminics also have a sedative action, and this can be troublesome sometimes. Newer antihistaminic drugs are claimed to be non-sedative however they are mildly sedative. They are also generally more expensive.

PreparationsofAntihistaminics

1st generation: Sedative: promethazine, diphenhydramine, dimenhydrinate.

Lesssedative: Chlorpheniramine, pheniramine, chlorcyclizine.

2nd generation: Non-sedative:loratidine, cetrizine.

ActionsofAntihistaminics

They prevent or stop (block) the actions of histamine in different parts of the body, thus resulting in the following effects:

- Prevent or reverse the decrease in size of respiratory passages.
- Reduce the effect of low blood pressure.
- Reduce itching, pain and feeling of warmth.
- Decrease sensation of vomiting (nausea) and other symptoms of travel sickness.
- Produce sedation and drowsiness leading to sleep, due to their action on the nervous system.
- Drying of the mouth, throat and nasal passages.

Side-EffectsofAntihistaminics

Sedation and drowsiness: these are more common than the other side-effects. Persons taking these drugs should not drive vehicles, operate machinery or perform tasks that require full mental alertness. Other related effects like tiredness and lethargy may also be seen. This effect is increased when alcohol or other sedative drugs are taken at the same time.

- Sensation of vomiting (nausea), vomiting and abdominal pain.

- A decrease in blood pressure (hypotension) and feeling of tightness in the chest.
- Dryness of mouth, throat and nasal passages.
- Blurring of vision.
- Difficulty in urination.

The side-effects are more common in older adults.

Uses

- Allergic conditions
- Reactions due to drugs, insect bites, chemicals.
- Hay fever, seasonal allergy, dry cough.
- Hives (urticaria).
- Itching (pruritus) associated with various skin diseases like eczema and dermatitis however the cause of the itching (if any) should be treated as well.
- Sedation to calm patients in certain situations.
- To prevent nausea and vomiting.
- To prevent travel sickness associated with travel on land and sea.
- To prevent dizziness (vertigo).

Precautions

- Alcohol should be avoided while taking these drugs.
- Other sedative and sleep-inducing drugs will increase the sedation produced by antihistaminics.
- These drugs should be avoided in pregnancy and breast-feeding mothers.
- Driving a vehicle, operation of machinery and any other task requiring mental alertness should be avoided while taking these drugs.
- They should not be given to children under two years of age.
- They should be used with caution in patients already having prostate disease, glaucoma and liver disease.

Misuse

- To treat the common cold they produce a drying out of the throat and nasal passages which is not helpful in this situation.
- To prevent allergic reactions eg. before giving a blood transfusion this is common in some hospitals.
- To treat itching (pruritus) without treating the cause as well.

11. Anti-Hypertensive Drugs

Hypertension is a condition where there is an abnormally high blood pressure. The normal blood pressure in the cardio-vascular (circulatory) system varies constantly. It rises to a peak (which is called the systolic pressure) soon after the contraction of the main chambers (ventricles) of the heart. It then falls to a lower level just before the next contraction (which is known as the diastolic pressure). Hence a person's blood pressure is represented by two numbers - the systolic first and the diastolic second. These numbers indicate the pressure in terms of the height (in millimetres) a column of mercury would be pushed up by the blood pressure. This principle is used in the form of an instrument called the sphygmomanometer, which is used to measure the blood pressure.
Apart from the variation between systolic and diastolic levels of blood pressure, there are also variations in other conditions like physical exercise, stress, anxiety, emotional changes and other factors. Hence a simple measurement of high blood pressure is not always indicative of hypertension - it needs to be repeated at different times under resting conditions.

The blood pressure is related to the volume of blood pumped out, the force of contraction of the heart and also the resistance of the larger blood vessels. The extra volume of blood pumped out by the heart is normally adjusted by the larger arteries, which are elastic. However, if the arteries are rigid or stiff or narrowed by disease, the blood pressure within them will rise higher with every contraction of the heart.

Therearetwomajortypesofhypertension:

1. Primary hypertension - where there is no clear cause for the rise in blood pressure.
2. Secondary hypertension - the rise in blood pressure is due to diseases of the kidney, endocrine glands and abnormalities of some blood vessels.

Normal blood pressure is considered to be below 130 mm systolic and 85 mm diastolic.

Hypertension cannot be ignored as its complications are serious and cause death and severe disability - more than any other types of diseases. Continuously raised blood pressure damages blood vessels. Atherosclerosis, a disease of arteries in which there is a hardening along with the deposition of fatty substances on their inner surfaces, is aggravated by hypertension. Coronary thrombosis and stroke are the fatal results of the process, in the arteries of the heart and brain. However, high blood pressure may also damage the heart, eyes and kidneys.

Hypertension should be looked for in every adult with regular checks as part of a physical examination. If detected early, the risk of developing complications can be decreased with treatment with drugs and other measures. Anti-hypertensive drugs are safe and effective.

TypesandActionofAnti-HypertensiveDrugs

There are numerous anti-hypertensive drugs, acting through different mechanisms to decrease blood ressure. There are three main groups of anti-hypertensive drugs:

Beta-blockers - these drugs interfere with the nervous and hormonal regulation of the heart, slowing he heart and making it contract less forcefully. These actions result in a decrease of blood pressure. Examples of drugs in this group include propranolol, atenolol, etc.

Vasodilators- these drugs act on the arteries to relax them. They act in different ways. This group includes the ACE inhibitors, the calcium channel antagonists and the alpha blockers. Examples of drugs in this group are amlodipine, captopril, enalapril.

Diuretics- they act on the kidneys, causing an increased flow of water and salt in the urine, thus bringing down the blood pressure. Examples of drugs in this group are hydrochlorothiazide.

Side-EffectsofAnti-HypertensiveDrugs

The side-effects of anti-hypertensive drugs are numerous. These important and serious side-effects should be kept in mind while using them:

- General reactions: Nausea, vomiting, headache, fatigue, giddiness, weakness, loss of appetite (anorexia), loss of sense of taste, muscle cramps.
- Allergic reactions: joint pains, skin rashes, fever.
- Circulatory (cardiovascular) system: decrease in blood pressure in the erect posture, slowing or increase in the heart rate (bradycardia or tachycardia), palpitations.
- Digestive (gastro-intestinal) system: constipation, jaundice, diarrhoea, aggravation of peptic ulcer disease.
- Neurological effects: sedation, drowsiness, forgetfulness, change in sleep habits, mental depression.
- Blood abnormalities: changes in white blood cells.
- Hormonal (endocrine) effects: impotence, enlargement of the breasts in males (gynaecomastia).
- Other effects: dryness of the mouth or excessive salivation, retention of salt and water (leading to weight gain), tolerance to the anti-hypertensive action, blocking (congestion) of the nose, decrease in salt levels (eg. potassium).

PrecautionswithAnti-HypertensiveDrugs

There are a number of conditions or diseases where some anti-hypertensive drugs should be used with caution or not at all. These should be checked for before starting treatment. Some of these conditions are:

- Psychiatric conditions: mental depression.
- Cardiovascular conditions: angina, heart failure, previous heart attack (myocardial infarction), enlargement of the heart, slow heart rate, palpitations.
- Endocrine (hormonal) conditions: increase in thyroid hormone secretion, diabetes.
- Gastro-intestinal conditions: peptic ulcer.
- Respiratory conditions: asthma.
- Pregnancy.
- Others: retention of water and salts, weakening of the bones (osteoporosis), kidney stones.
- Interaction with other drugs eg. anti-depressants, digitalis, steroids.

UseofAnti-HypertensiveDrugs

The treatment of hypertension requires a change in lifestyle and anti-hypertensive drugs only if necessary. The measures to bring about a change in lifestyle include the following:

a. Smoking should be stopped.
b. Regular physical exercise such as brisk walking should be done everyday.
c. Weight reduction to the recommended level (according to the individual's height).
d. Reduction of salt intake in food.
e. Reduction of oils and fats in food.
f. Reduction in alcohol consumption.
g. Decrease in stress, increase in activities promoting relaxation.

It is often found that these measures by themselves can bring about a significant lowering of blood pressure, making drug treatment unnecessary.

A complete initial physical examination of a hypertensive patient is essential. This includes repeated readings of blood pressure in different body positions (lying down and standing usually), urine and blood examinations, X-ray, ECG and an ophthalmological examination. Other more complex tests may be sometimes required.

The treatment of hypertension with drugs, if required, will almost certainly have to be life long. The success of the treatment depends mainly on the time and attention given by the doctor, and to the co-operation of the patient.

Anti-hypertensive drugs are often used alone, especially in mild cases. However, combinations of these drugs are used to achieve better results and to decrease the possibility of side-effects. Two or more drugs acting by different mechanisms are often given at the same time, rather than drugs acting by the same mechanism.

Treatment of hypertension in the elderly (above 60 years) needs extra care. Anti-hypertensive drugs causing mental depression, fall of blood pressure in the standing or erect position and other potentially serious side-effects should be avoided.

- Hypertension should not be ignored as it may cause potentially serious or fatal complications.
- A complete physical examination with laboratory tests is essential in all new hypertensive patients.
- Lifestyle changes are very important in the management of hypertension especially stopping smoking, reduction of weight and physical exercise.
- Effective drugs are available which in most cases have to be taken life-long.
- Treatment of hypertension in the elderly needs extra care.

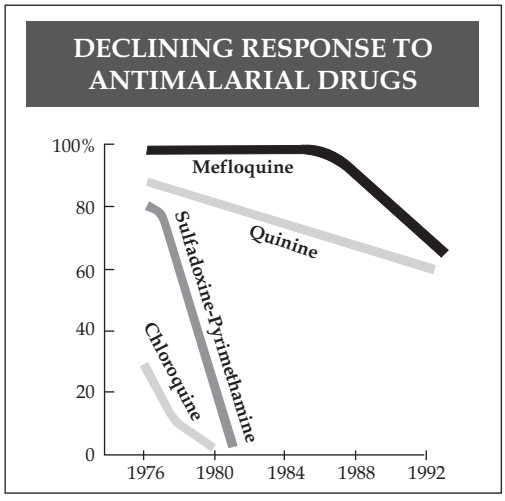
12. Antimalarial Drugs

Malaria is an infectious disease caused by the plasmodium parasite. The disease is an important public health problem in many parts of the world. Currently malaria is present in 107 countries of the world with about 3.2 billion people at risk. There are estimated to be about 350 to 500 million cases annually worldwide, with 1 to 2 million deaths.

There are four varieties of the malaria parasite - *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium malariae*, and *Plasmodium ovale*. Of these four, *Plasmodium vivax* and *Plasmodium falciparum* account for almost all the malaria in India. The disease is spread by the female Anopheles mosquito.

When a healthy person is bitten by an infected Anopheles mosquito, the parasite is injected into the body with the saliva of the mosquito. These parasites travel through the blood to the liver, where they develop and multiply for about 10 days. After this stage they enter the blood stream, where they penetrate the red blood cells (RBCs) and grow and multiply in them. After two or three days, the parasites break out of the RBCs and individual parasites attack fresh RBCs. It is at this point that the characteristic signs and symptoms of an attack of malaria are seen. The process repeats itself with the parasites breaking out of the RBCs every two or three days and infecting fresh RBCs. Some of the parasites develop into forms which are infective to mosquitoes.

The main symptom of malaria is usually fever with chills; other symptoms are often present. The fever of malaria is typically in three stages - a cold stage, a hot stage and a sweating stage, in that order. The fever recurs every two or three days. Other symptoms include headache, nausea, vomiting, feeling of weakness, and loss of appetite. Symptoms of severe malaria (usually caused by *P. falciparum*) include jaundice, very high fever, difficult breathing and blood in the urine. Loss of consciousness, convulsions and irrelevant speech indicates a condition known as cerebral malaria, in which the brain is involved. This condition is usually fatal unless treated promptly. Malaria is especially serious in children and in pregnant women. In children it causes anaemia and malnutrition, and in combination with other diseases can cause death. In pregnant women malaria causes anaemia, abortion, premature birth and low birth weight, giving rise to increased maternal and infant mortality. In recent years, malaria has become difficult to treat in some areas because of the resistance of the malaria parasite to the action of the more commonly used antimalarial drugs, especially chloroquine. This resistance is caused by irregular and incomplete treatment, and requires the use of more powerful and expensive drugs, sometimes given in combination.



Source: The Southeast Journal of Tropical Medicine and Public Health, Mekong Malaria*, Volume 30, Supplement 4, p.68, 1999.*

Types of Antimalarial Drugs

There are several drugs used in the treatment of malaria. They work in different ways, and are sometimes given in combination to increase their effectiveness. Some drugs (eg., primaquine) are only used in certain situations.

The different types of antimalarial drugs are as follows:

Drugsusedtotreatanattackofmalaria

- Older drugs: Quinine, chloroquine, sulphadoxine - pyrimethamine combination, proguanil, dapsone.
- Newer drugs: mefloquine, halofantrine, artemisinin derivatives.

The newer antimalarial drugs are mainly used to treat malaria resistant to the action of the commonly used older antimalarial drugs (drug resistant malaria). This drug resistance is mainly found in infections with the *P. falciparum* parasite.

Drugsusedforotherpurposesinmalariatreatment

- Prevention of relapse - primaquine.
- Prevention of spread from one person to another - primaquine.
- Prevention of an attack of malaria - doxycycline.

ActionsofAntimalarialDrugs

Most antimalarial drugs act on the malarial parasite in the blood - they kill the parasite during this stage of the disease. These drugs include quinine, chloroquine, sulphadoxine-pyrimethamine combination, mefloquine, artemisinin derivatives etc.

Other antimalarial drugs act on the malaria parasite in other ways:

1. In the liver, so that the malaria parasites there are destroyed (eg., primaquine).
2. In the blood on the forms of the parasite infective to mosquitos (eg., primaquine).
3. To prevent infection by the malaria parasite and thus prevent the disease (eg., doxycycline)

Side-EffectsofAntimalarialDrugs

- Sense of vomiting (nausea) and vomiting - this is seen especially when antimalarial drugs are taken on an empty stomach. Hence these drugs should always be taken after food.
- Pain in the stomach (abdomen) with cramps, ringing in the ears, headache and dizziness.
- Allergic reactions - itching, rashes, swelling (oedema) of parts of the body, sensitivity, to light (photosensitivity).
- Other skin problems: severe itching, bleaching of hair of the scalp, eyebrows and eyelashes.
- Heart and blood vessels: some antimalarial drugs depress the functioning of the heart and enlarge the blood vessels, thus causing a fall in blood pressure (hypotension).
- Blurring of vision, double vision, disturbance of colour vision and damage to the eye may occur with some antimalarial drugs when taken over a long period of time.
- Metabolic actions: some antimalarial drugs decrease the level of glucose in the blood - causing a condition known as hypoglycaemia.
- Behavioural effects: abnormal behaviour, depression and psychiatric disturbances occur with some antimalarial drugs.
- Effects on the blood: several antimalarial drugs can affect the various cells of the blood (red and white blood cells) in different ways and sometimes cause anaemia.

UsesofAntimalarialDrugs

1. Treatment of an attack of malaria - most antimalarial drugs are used to treat attacks of malaria. They are usually given by mouth (orally) in the form of tablets or syrups.

   Some antimalarial drugs are available for use as injections. These are to be used only in certain situations, eg., when a patient is vomiting and unable to take drugs by mouth, or when the patient is unconscious. These drugs are usually given only in a hospital or health centre.

2. Prevention (prophylaxis) of malaria - Certain people need to take antimalarial drugs to protect themselves from getting malaria. Other protective measures should also be used at the same time eg., impregnated mosquito nets, mosquito repellents etc.

3a. Travellers and tourists coming from areas with little or no malaria to an area where malaria is common.

3b. Pregnant women in areas where malaria is common - antimalarial drugs taken regularly during their pregnancy will protect them from the severe effects of malaria in pregnancy.

All other persons should not take antimalarial drugs to prevent malaria. This is because antimalarial drugs cause side-effects (some of which are serious) when taken for a long time. Also, in those persons living in an area where malaria is common, taking antimalarial drugs to prevent malaria for prolonged periods of time can cause resistance of the malaria parasite to the drugs (drug resistance).

PrecautionswithAntimalarialDrugs

1. Pregnancy and breast-feeding mothers - some antimalarial drugs should be avoided in pregnancy and in mothers breast-feeding their children.

   However, the common antimalarial drugs chloroquine and quinine are completely safe in pregnancy when given in the recommended doses for treating malaria.

2. Certain genetic diseases of the blood (eg., G6-PD deficiency) - some antimalarial drugs should not be used in persons having these conditions.

3. Injectable antimalarial drugs should be used with caution, and preferably only in a health centre or hospital.

   Some injectable antimalarial drugs eg.,, chloroquine are very dangerous in children, and can sometimes be fatal. Their use should be avoided as far as possible.

4. Correct and complete treatment must be ensured to avoid a relapse, and the development of resistance of the malaria parasite to antimalarial drugs.

5. The newer antimalarial drugs (eg., mefloquine, halofantrine and the artemisinin derivatives should be reserved for use in cases of malaria resistant to the older drugs (drug resistant malaria). They should not be used routinely for all cases of malaria.

- Antimalarial drugs work in different ways and should be given carefully.
- Antimalarial drugs should not be routinely used for the prevention of malaria.
- Injectable antimalarial drugs are to be used only when drugs cannot be taken by mouth.
- Correct and complete treatment must be ensured to avoid a relapse or development of drug resistance.

13. Antituberculosis Drugs

Tuberculosis (TB) is a chronic infectious disease caused by the bacteria *Mycobacterium tuberculosis*. It affects different parts of the body like the lungs, lymph glands, joints, bones, skin, the membrane covering the brain etc. However, the lungs are affected most frequently.

Tuberculosis is spread by droplets, which contain the tuberculosis bacteria. These droplets are coughed out by a person who has tuberculosis of the lungs. Such persons who have not taken treatment are infectious to others.

The chief symptoms of tuberculosis are any of the following:

- Cough - with or without sputum - for more than three weeks.
- Fever - usually low grade - for more than three weeks.
- Chest pain.
- Blood in the sputum.
- Swelling of a joint or along the spine.
- Painless swelling of lymph glands in the neck.
- Weight loss, malnutrition in children.
- Stiffness of the neck.

Tuberculosis is diagnosed most commonly by a sputum test where the presence of the tuberculosis bacteria is checked. Other tests used for the diagnosis of tuberculosis include X-ray, examination of certain body fluids and tissues (biopsy), and the Mantoux's test in children.

The treatment of tuberculosis is long and spread over several months. This is because the bacteria are often present within body cells and tissues, and drugs need to penetrate these to reach the tuberculosis bacteria.

There are several drugs available for the treatment of tuberculosis. Usually, antituberculosis drugs are not given alone (singly) but in combination of two or more drugs together at the same time. This is to avoid the development of drug resistance. The combination of drugs given in a particular dosage for a particular length of time is known as a drug regimen.

Only a certain number of regimens are approved (by the World Health Organization and other international bodies) and only these should be used by all medical practitioners.

Tworecentandseriousdevelopmentsinthetuberculosissituationare:

- The development of drug resistance of the tuberculosis bacteria (when the tuberculosis bacteria become resistant to the action of antituberculosis drugs), leading to **multi-drug resistant (MDR) tuberculosis**. This is caused by irregular, incorrect and incomplete treatment of the disease.
- **TheHIV / AIDSepidemic** has caused a large increase in the number of patients of tuberculosis. The human immunodeficiency virus decreases immunity and makes the patient susceptible to other infections, the most common of which is tuberculosis.

TypesofAntituberculosisDrugs

Antituberculosis drugs are of two types:

First line or standard antituberculosis drugs - rifampicin, isoniazid (INH), pyrazinamide, ethambutol, streptomycin.

Second line or reserve antituberculosis drugs - kanamycin, cycloserine, ethionamide, ciprofloxacin, ofloxacin, para-amino salicylic acid (PAS), capreomycin.

ActionsofAntituberculosisDrugs

The drugs are either bactericidal (kill the tuberculosis bacteria) or bacteriostatic (prevent the growth and multiplication of the tuberculosis bacteria). The drugs act in different ways on the structure and function (including metabolism) of the tuberculosis bacteria. Antituberculosis drugs are never given singly as this leads to the rapid development of drug resistant tuberculosis bacteria.

Side-EffectsofAntituberculosisDrugs

Antituberculosis drugs cause side-effects in some persons. Any of the following side-effects may be seen. Some of these side-effects are seen with a particular drug only:

- General symptoms like loss of appetite (anorexia), sensation of vomiting (nausea), vomiting, diarrhoea, abdominal pain, joint pains and headache.
- Allergic reactions including generalised itching (pruritus), skin rashes, swelling of lymph glands, fever and jaundice. These are more frequent in HIV +ve patients. Occasionally allergic reactions can be severe leading to shock and collapse.
- Inflammation of the liver (hepatitis) with symptoms and signs such as jaundice, enlargement of the liver, pain in the abdomen etc. This side effect is seen more frequently in older patients (above 50 years of age).
- Nervous system involvement (central or peripheral) - nerves are inflamed causing symptoms of tingling, numbness, burning and pain along the nerves. The nerve to the eye (optic nerve) may be involved leading to changes in vision. Confusion, delusions, momentary loss of memory, difficulty in sleeping (insomnia) and hallucinations are seen. Abnormal behaviour is also seen with some of these drugs.
- Discolouration of the body fluids like urine, sweat, tears, saliva and sputum.
- Damage to the sense of balance and sense of hearing - due to the involvement of the 8th cranial nerve.
- Damage to the kidneys and their function.

PrecautionswithAntituberculosisDrugs

Antituberculosis drugs should be used with caution in certain situations:

- Previous allergy to a particular drug.
- Persons with liver disease.
- In pregnancy and in mothers who are breastfeeding their infants.
- Patients taking certain other drugs such as steroids, phenytoin (anti-convulsant), sulphonylureas (anti-diabetic), dapsone (for leprosy and other skin diseases), digoxin (for certain conditions of the heart) should know that the action of these drugs are often reduced or enhanced by some antituberculosis drugs.

- Regular eye examinations may be required to detect damage to the optic nerve.
- In patients with a history of epilepsy and psychiatric illness, antituberculosis drugs should be taken with care.
- Persons taking these drugs should avoid alcohol.

UseofAntituberculosisDrugs

Antituberculosis drugs are used in combination of two or more in the treatment of tuberculosis. The combination of drugs given in a particular dosage for a particular period of time is known as a drug treatment regimen.

Only a few regimens are approved for use and all medical practitioners must follow these.

Treatment of tuberculosis with antituberculosis drugs consists of an initial intensive phase of two or three months duration, using three or four drugs. This is followed by a continuation phase where two drugs are given for a further period of four to six months. The total duration of treatnent in most cases is six to nine months. However, certain forms of tuberculosis require treatment for a longer duration - upto twelve to eighteen months.

Vitamin B_6 (pyridoxine) is given along with antituberculosis drugs to prevent inflammation of the peripheral nerves.

Multi-drug resistant (MDR) tuberculosis, is difficult to treat. The second line or reserve antituberculosis drugs have to be used in this situation. These drugs are generally expensive, less effective, cause more side-effects and have to be taken for a longer duration than standard first line antituberculosis drugs. It is therefore very important to avoid or minimise the development of drug resistance. This is done by ensuring correct and complete treatment of all tuberculosis cases with standard first line antituberculosis drugs.

DOTS

DOTS (Directly Observed Treatment - Short course) is a recent advance in the treatment of tuberculosis. The drugs are not given to the patient to take at home. Instead the patient is required to attend a clinic or treatment centre where all the antituberculosis drugs are administered under direct supervision of a health worker. This method ensures that the drugs are actually consumed, and minimises problems of irregular and incomplete treatment and the development of drug resistance.

The drug treatment regimens in DOTS involve administration of antituberculosis drugs in higher doses thrice a week. These regimens have been found to be effective.

- Anti-tuberculosis drugs are always given in combination known as drug treatment regimens.
- Only recommended regimens should be used to treat cases of tuberculosis.
- Drug resistance and the HIV/AIDS epidemic are serious problems for tuberculosis control.
- Correct and complete treatment of all cases of tuberculosis must be ensured.

14. Anti-Tussive Drugs

The act of coughing is a protective reflex by which the lungs are able to expel potentially dangerous semisolid material in the respiratory tract, and to prevent entry of unwanted matter.

In coughing, initially a deep breath is taken and the vocal cords are pressed tightly together. Then the diaphragm is forced upwards and compresses the air of the lungs. The vocal cords come apart suddenly so that a jet of air passes upwards from all parts of the lungs. This jet of air expels sputum, mucus or small foreign bodies.

Many respiratory diseases and conditions have cough as a prominent symptom, because of the production of large amounts of secretions in the respiratory tract. Other causes of cough include irritating substances in the air being inhaled, such as cigarette smoke, dust, pollen and chemicals. Infections of the nasal cavity, sinuses and throat, and certain diseases of the heart may also give rise to cough.

Thus there are two main types of cough:

- Productive (or wet), in which there is production of large amounts of sputum.
- Dry, in which there is little or no sputum.

The correct treatment of cough involves the treatment of its cause.

The drugs used in the treatment of cough are known as anti-tussives. These are used only to relieve symptoms of cough and do not treat the conditions that cause it. Anti-tussive drugs are of the following types:

1. Locally acting drugs on the throat: eg., syrups, lozenges, cough drops, and linctuses - these act by soothing sore (inflamed) throats, relieving congestion etc. They also increase the flow of saliva, which also has a soothing action.
2. Expectorants - these drugs increase the production (secretion) of fluids in the respiratory tract and so enable the thick sputum to be liquefied. Hence they are used in conditions where there is production of thick sputum. Examples of expectorants include potassium citrate and *vasaka*.
3. Cough suppressants - these act on the central nervous system and suppress the cough reflex. They are useful in relieving dry cough. They should not be used in patients who have productive coughs. An example of a cough suppressant is codeine.
4. Mucolytics - these drugs act directly on thick sputum and make it thin, thus enabling it to be coughed out more easily. An example of these drugs is bromhexine.
5. Others - drugs which act by dilating the smaller parts of the respiratory tract (bronchodilators) or by decreasing secretions in the respiratory tract (anti-histaminic and decongestant drugs). Examples of these drugs are salbutamol (bronchodilator) chlorpheniramine and chlorpromazine (antihistaminics).

Many cough syrups and other formulations available in the market contain a combination of the above types of anti-tussive drugs, and some others. Various studies have shown that the most common cause of cough is acute respiratory infections caused by viruses. This type of cough is temporary, self-limiting and does not need treatment.

Side-EffectsofAnti-tussiveDrugs

The centrally acting cough suppressants can cause constipation.

Anti-histaminic drugs may produce lethargy and drowsiness, especially in children.

Decongestants may cause inability to sleep (insomnia), sudden uncontrolled movements (dystonic reactions), hallucinations and nervousness.

PrecautionswithAnti-tussiveDrugs

1. Cough suppressants should not usually be used in patients with conditions where there is a productive cough. They are not recommended in young children.
2. Cough preparations containing anti-histaminics should not be used in conditions where there is thick sputum, as the action of anti-histaminics can dry up the sputum. As they may produce sedation, those driving or operating machinery should not use them.
3. Drugs for cough may be dangerous in sedated or semi-conscious patients.

UseofAnti-tussiveDrugs

Cough is a useful reflex action, which serves to clear the respiratory tract and is also a symptom of diseases of the lungs and heart. Cough syrups and other formulations available in the market contain a mixture of an expectorant, a cough suppressant, and anti-histaminic and a bronchodilator in a syrup form, with some flavouring added. Many of the actions of these ingredients are antagonistic (in opposition) with each other: eg., expectorants and anti-histaminics. Hence many of these preparations are irrational or of doubtful value.

For most common coughs (including those associated with the common cold), it is useful to remember the following:

- A mild cough usually does not require treatment.
- For mild infections of the nose and throat, simple remedies such as boiled sugar sweets, lemon drops, a mixture of lemon juice and honey will provide better relief than many cough lozenges and tablets. Anti-histaminics may be useful in these conditions to decrease the production of mucus.
- Other homemade remedies for cough are often better and safer than cough syrups available in the market, eg., a mixture of honey, ginger, lemon juice and brandy which is a "traditional" preparation.
- Water is the best expectorant for conditions where there is a production of large amounts of thick sputum. It is very important to keep the patient with these conditions well hydrated by drinking plenty of water and other fluids, so that the sputum may be coughed out easily.
- Other measures, which achieve the same effect, are keeping the patient's room warm and humid and advising simple steam inhalations from time to time.
- A dry irritating cough, which is worse at night and prevents the patient from sleeping, may be Suppressed with a cough suppressant alone.
- Cough and cold medicines are not useful in children and can sometimes be harmful.

- Cough is a useful protective reflex and removes unwanted material from the lungs.
- A dry, irritating cough may be suppressed.
- Water is a good expectorant for productive coughs.
- Home cough remedies are often better and safer than those available in the market.
- Cough syrups are not useful in children.

15. Antiviral Drugs

Viruses are the smallest of the microorganisms that cause disease, and have different structure as well. This structure consists of a core of nucleic acid (which may be either DNA or RNA) and a coat made of protein.

Viruses are of two types:

- Deoxyribonucleic acid (DNA) viruses eg., smallpox, hepatitis B, herpes simplex viruses.
- Ribonucleic acid (RNA) viruses eg., poliomyelitis, measles, yellow fever and HIV.

Viruses are different from bacteria and other microorganisms in that they can only grow and multiply in living cells. Hence it is difficult to find a drug, which can destroy viruses without also destroying the cells they grow in.

In recent times, many drugs have been evaluated for use in HIV infections. Some of these drugs used in combination slow down the virus multiplication, improve the functioning of the immune system and thus prolong life. These drugs are known as anti-retroviral drugs (ARV drugs) as the human immunodeficiency virus is a retrovirus.

TypesofAntiviralDrugs

- Drugs interfering with the synthesis of nucleic acids (RNA or DNA): for instance, acyclovir, ribavarin, idoxuridine, ribavarin and azidothymidine.
- Naturally occuring substances, eg., interferon.
- Others, eg., amantadine.
- Anti-retroviral (ARV) drugs - act against the human immunodeficiency virus (HIV).

ActionsofAntiviralDrugs

- Interfere with the synthesis of viral nucleic acid (RNA or DNA).
- Modification or alteration of other cells, which are required for viral growth and multiplication.
- Interference with multiplication of viruses.

UsesofAntiviralDrugs

Antiviral drugs are used in the treatment of certain viral infections. Some of these infections are as follows:

- Herpes simplex infection - especially of the eye. The drugs may be used locally or given orally or intravenously.
- Herpes zoster infections - antiviral drugs are useful when there is encephalitis. Treatment should be started as possible after the patches appear on the skin.

- Cytomegalovirus (CMV) infections of the eye and the large intestine (colon) - these infections are commonly seen in patients with AIDS.
- Influenza A and B infections - the antiviral drugs are used both in the prevention and treatment of influenza.
- Hepatitis B, C and D infections - they can prevent progressive liver damage.
- HIV infections - drugs used to treat HIV/AIDS, also known as anti-retroviral (ARV) drugs are given in combination to treat or prevent HIV infections in the following situations. They are not a cure but are useful in prolonging the life of severely ill patients.

a. Long term suppression of HIV - the combination of two or more anti-retroviral drugs (to prevent or delay the development of resistance) can decrease virus multiplication which leads to improvement of immunity and decrease in symptoms and complications of HIV infections. There are different regimens (combination of drugs) recommended and the choice of a particular regimen depends on the convenience and tolerance to the side-effects of the drugs.

Patients receiving these drugs require careful monitoring. This includes a detailed medical history, the identification of existing and previous illnesses related to HIV, and the identification of co-existing medical conditions (such as pregnancy). Laboratory tests that are required are haematological tests (especially white blood cell counts), biochemical tests and others (eg. pregnancy tests).

The treatment should be started as early as possible before the patient's immune system is permanently damaged. At the same time, the toxic effects of the drugs should be carefully watched for.

b. Prevention of infection in individuals exposed to HIV - this is known as Post-Exposure Prophylaxis (PEP). It consists of anti-retroviral drug treatment given as soon as possible after an accidental exposure to HIV. This accidental exposure occurs in health professionals and other health workers while handling HIV+ve patients.

c. Prevention of spread of HIV from mother to child (foetus) during pregnancy - anti-retroviral drugs are given to the pregnant mother in full doses as early as possible in pregnancy. The newborn child should also be treated for the first few weeks of life.

If a pregnant woman is detected to be HIV+ve at the end of pregnancy, she should still be given anti-retroviral drugs, and the infant should be given these drugs for atleast a week. This treatment will prevent the progression of disease in the mother and spread of HIV to the infant at birth.

Conclusion

Antiviral drugs are still at an early stage of use and development.

16. Laxatives

A person is said to be suffering from 'constipation' if he/she passes dry, hard stools less frequently than usual (once a day).

Constipation can be acute or chronic.

a) *Acute Constipation*: It may develop suddenly. It could be a part of a more serious illness especially if the patient also suffers from abdominal pain, vomiting and bloating. Such patients should consult the doctor immediately.

b) *Chronic Constipation*: It is the long-standing type of constipation and it occurs due to various reasons:

1. Faulty bowel habits - habitually not attending to the nature call in time.
2. Faulty diet that is low in roughage, fiber or water content. The simple remedy is more fluid and a diet that contains plenty of foods that are high in fibre. Avoid constipating foods.
3. Lack of exercise.
4. Painful lesions in the anal region such as cracking of skin near anal region (anal fissure).
5. Diseases of the bowel: Constipation may also occur following an attack of diarrhoea or the day after taking a laxative. This needs no treatment.

Constipation that occurs due to certain drugs, e.g., narcotic analgesics, antacids (containing aluminium), tricyclic antidepressants, or constipation that occurs due to certain disease, e.g., hypothyroidism (decreased production of thyroid hormones) and scleroderma (hardening of skin due to chronic inflammation), get cured once the causative drugs are stopped and the causative disease is cured.

Constipation is very common in :

a) Old people - due to lack of exercise. It could also be a sign of some serious disease (e.g., cancer). The doctor should be consulted about any persistent change in the bowel habit.

b) Pregnant women - because of difficulty in using abdominal muscles during evacuation. Increase in fluid intake as will as high fibre food intake can prove helpful. Take doctor's guidance if the problem is too severe.

GeneralGuidelines

An important point to be remembered is that many patients with normal stools and normal frequency of defecation imagine that they are constipated. They need reassurance and no drug treatment. Patients with acute (suddenly developed) constipation should consult the doctor for the diagnosis of the underlying cause.Patients with chronic constipation need bowel training. They must spare some time regularly every morning to visit the toilet. They should also drink plenty of water, eat leafy vegetables and fiber food with high fiber content. Besides this, they should also take physical exercise, such as walk for half to an hour daily. Laxatives such as senna and isphagulla can be used for short periods and then slowly stopped (suddenly stopping use of a laxative may cause recurrence of constipation).

Whenshouldalaxativebeused?

A laxative should be used for short periods only as its long-term use is harmful.

It is mainly used:

a) in elderly bed-ridden patients suffering from constipation due to lack of exercise.

b) to clear the bowel and investigative procedures, e.g., colonoscopy.

c) to prevent pain and straining (i) in people with hernia (ii) in people with piles (iii) after childbirth and (iv) after abdominal surgery.

Typesoflaxatives

1. *Bulk forming laxatives:* They absorb water in the bowel thereby increasing the volume of faecal matter and making stools softer and easier to pass. They are slow acting and less likely to interfere with normal bowel action as compared to other laxatives they may cause intestinal obstruction and hence should be taken after doctor's consultation by people suffering from constipation with abdominal pain, e.g., Isphagulla (isabgol), methylcellulose.
2. *Stimulant (contact) laxatives:* They cause the bowel muscle to contract, increasing the speed with which faecal matter passes through the intestine. They are fast acing and used only when other treatments have failed. They may cause abdominal cramps and diarrhoea and should normally not be used for more than a week, e.g., bisacodyl, docusate, phenolphthalein, senna.
3. *Lubricants:* It makes the bowel movements softer and easier to pass without increasing the bulk. It is used when hard bowel movements cause pain on defecation, e.g., piles and also in elderly people. Prolonged use causes coating which can interfere with absorption of certain essential vitamins, e.g., liquid paraffin.
4. *Saline laxatives*: They prevent water from passing out of the large intestine without increasing the bulk of the faeces. They are used to clear the bowel before surgery or investigative procedures. They are not preferred for long-term relief or constipation as they cause chemical imbalances in the body, e.g., Epsom salt (magnesium sulfate).
5. *Lactulose:* It causes fluid to accumulate in the intestine. It is used for long-term treatment of chronic constipation as an alternative to bulk forming laxatives. It may cause stomach cramps and flatulence (gas).

Precautions

- Do not use a laxative frequently to treat constipation as habit may be formed.
- Laxatives can cause diarrhoea if taken in overdose and constipation if overused.
- Discontinue use of laxative slowly as soon as normal bowel movements are re-established.
- Do not use laxatives to treat constipation associated with fever or following heart attack.
- Do not use laxatives in children except special circumstances on the advice of a doctor.

Consult a doctor in the following cases:

- A patient has constipation with vomiting, fever and has not even passed wind (gas).
- Chronic constipation with no improvement after two weeks treatment.
- Unexplained constipation in elderly.
- Persistent constipation in children.
- Persistent pain in stomach or blood in stools or pain during evacuation.

CombinationProducts

Many times laxatives are combined with anthelmentics (drugs that expel worms). This combination is irrational and has no benefit over single product containing only anthelmentic.

17. Steroids

Introduction

Steroids (also known as corticosteroids) are an important, useful and potent group of drugs. They are found in the body naturally as hormones, being secreted by the adrenal glands. They have many different actions in the body, involving the immune response, water and mineral metabolism, anti-inflammatory action, etc.

TypesofSteroids

Natural: found in the body as hormones, e.g., hydrocortisone, corticosterone, aldosterone.

Synthetic: human-made (artificially made in laboratories) steroids, used as drugs, e.g., prednisolone, betamethasone and dexamethasone.

They may be given orally or by injections, by inhalation in the form of aerosols, or used locally in the form of ointments or creams.

PreparationsofSteroids

1. Oral: Short acting - Cortisone
   Intermediate - Prednisone
   - Prednisolone
   Long acting - Dexamethasone
   - Betamethasone
2. Topical (for application to skin):
   Low potency - Hydrocortisone
   Medium potency - Betamethasone, Fluocinolone, Beclomethasone, Triamcinolone
   High potency - Clobetasol
3. Inhalation (oral or nasal route):
   Budesonide, Beclomethasone.
4. Intravenous: Hydrocortisone, Dexamethasone, Betamethasone.

FunctionsandActionsofSteroids

Metabolic actions - they influence the metabolism of carbohydrates, fats, proteins, minerals and water. They raise the level of glucose in the blood, and increase the breakdown of tissues (resulting in wasting). The fat in the body is re-distributed in the neck, shoulders and face. Salt (sodium chloride) is retained in the body. Calcium absorption is reduced, and this influences bone structures.

Anti-inflammatory action - they prevent or suppress the features of inflammation such as pain, swelling, local warmth and redness. Thus there is marked relief of these symptoms in inflammatory conditions such as rheumatoid arthritis. However the cause of the inflammatory reaction is not controlled. This effect can be also be seen when steroids are applied locally in the form of a cream or ointment for certain inflammatory skin conditions, e.g., eczema.

Anti-allergic action - steroids suppress the body's allergic response (response to foreign substances) directly, as well as by their anti-inflammatory action.

Anti-immunologic action - steroids suppress the body's natural immune mechanism against infection, and so increase the susceptibility of the body to various types of infection (bacterial, viral, fungal and parasitic).

Suppression of natural hormones Steroids given in high doses for prolonged periods cause a decrease in the secretion of the natural steroids in the body.

Side-EffectsofSteroids

The side-effects of steroids are frequent and should be checked for in every patient taking these drugs:

- Ulceration of the stomach - may occur even with a few days of treatment.
- Swelling of neck, face and obesity due to fat deposition.
- Weakening of the bones leading to fractures (a condition called osteoporosis).
- Glaucoma and cataract formation may occur in some patients using steroid drops in the eye.
- Raised blood pressure (hypertension), swelling of the body (oedema).
- Symptoms and signs of diabetes.
- Decrease (retardation) of growth in children.
- Masking (suppression) of signs and symptoms of serious infection.
- Changes in body hair - increase in body hair, loss of scalp hair may be seen.
- Delayed wound healing.
- Aggravation (increase in severity) of skin infections when applied locally.
- Skin changes may be seen on local application, especially when potent steroids are used - thinning of skin, lightening of skin colour, easy bruising.
- Suppression of production of natural steroids in the body this is seen more on prolonged or high dosages of steroids.

UsesofSteroids

- In Addison's disease, a condition where insufficient or no natural hormones are produced in the body.
- In certain life threatening emergencies, when it is necessary to suppress the inflammatory response of the body temporarily, e.g., acute allergic reactions, acute asthma not responding to ordinary drugs.
- In certain other acute and chronic inflammatory conditions, e.g., acute rheumatic fever, leukemia and some other cancers, pemphigus and some other skin diseases, and rheumatoid arthritis.
- In certain inflammatory/allergic skin, eye and ear conditions, e.g., eczema, psoriasis, and some types of inflammations of the eye.

PrecautionswithSteroids

a) They should be used with caution in patients with a previous history of stomach ulcers.

b) Tuberculosis should be excluded before starting a patient on steroids.

c) The patient's urine should be checked for sugar and the drug used with caution in diabetic patients.

d) The patients' weight and blood pressure should be monitored regularly.

e) The treatment with steroids should not be stopped abruptly, especially with high doses or after prolonged treatment, as the production of natural steroids in the body is suppressed. The dosage should be decreased gradually (ie. tapered).

f) Any infection present should be treated simultaneously.

g) If surgery is required or the patient develops an acute infection, the dose of the steroid may have to be increased.

h) Topical steroids should be used with caution, especially those of the high potency group. Prolonged use should be avoided, especially on the face.

MisuseofSteroids

Steroids are some of the most misused drugs in our country. The most common types of misuse are:

- To produce a rapid relief of symptoms like fever, body ache, etc., in common infections - this is the most common type of misuse.
- In the absence of a diagnosis, to produce symptomatic relief.
- In the treatment of inflammatory conditions of the skin, when steroids are combined with antifungal agents or antibiotics in the same preparation, for example, betamethasone with neomycin.

Conclusion

Steroids have many side-effects, some of them very dangerous. However, when used carefully, they are a very useful group of drugs. They can be life-saving in certain situations.

- **Steroids** are an **important and useful** group of drugs.
- They have many side-effects and are **harmful** if used incorrectly.
- They can be **life-saving** in some emergencies.
- **Misuse** of steroids is very common.

Annexure 2

Poisoning and its Treatment

We discuss here about poisoning because of its relation to poisoning by drug intake.

Poisoningmaybeduetotheingestionof

- Poisonous chemicals including overdose of high-danger drugs (see Box 12 below) or overdose of low-danger drugs in people highly allergic to them.
- Poisonous plants
- Contaminated food

Poisoning may occur intentionally (as a suicide attempt) or accidentally (especially in children and the elderly people).

HowtoRecognisePoisoning?

Occurrence of one or more of the following danger symptoms suggest poisoning:

- Drowsiness or unconsciousness
- Shallow, irregular or stopped breathing
- Vomiting
- Fits or convulsions

AlwaysRemember(inallcasesofpoisoning)

- A calm person should stay with the victim and observe him/her carefully, while others seek help.
- Arrange for an ambulance to transport the victim to the hospital.
- Call (phone) the doctor, give him/her details about the case (that is,. causative substance ingested and its amount, age of the victim), and follow his/her directions carefully.
- Keep the leftover substance along with its container (if any) that caused poisoning.
- Collect all evidence that will prove helpful in the correct diagnosis.
- In case you have to treat the victim yourself before medical help arrives, follow the treatment chart.

TreatmentofPoisoning

The chart presented below will help you to assess the situation and to determine your priorities. *The instructions given here, apply to all types of poisoning and not only drug-poisoning.* Also refer to the column 'Gross overdosage' in individual drug profiles (specific information on the symptoms likely to occur is given, where necessary, that is, in high-danger drugs).

TREATMENT CHART

Person is vomiting? ⟶ Yes ⟶ **Box 1** ⟶

1) Preserve the vomit for detection of poison in the hospital.

(2) Dilute the poison in stomach only if advised (Box 7)

(3) Lay the victim on his back on a firm surface and clear his mouth of any vomit/foreign material, which would otherwise block the air ways. Remove false teeth.

(4) Then lay the victim in the recovery position (Box 5) and get medical help.

↓ No

Person is conscious? ⟶ Yes ⟶ **Box 2** ⟶

1. In certain cases, it may be advisable to induce vomiting in the victim (Box 6). It must be attempted only when specifically advised.

2. Never induce vomiting if the victim is unconscious or if you suspect the poison to be a corrosive (acid or alkali) or a petroleum product.

3. Then follow steps 1 to 4 in Box 1.

↓ No

Person is Breathing? ⟶ Yes ⟶ **Box 3** ⟶

1. Do not induce vomiting
2. Then follow steps 3 and 4 in Box 1

↓ No ⟶ **Box 4** ⟶

1. Give artificial respiration (Box 6) and, if necessary, cardiac compression (Box 9).
2. Get medical help.

Box 5

RecoveryPosition

The recovery position is the safest position for an unconscious or drowsy person. It allows the person to breathe easily and will help to prevent choking if vomiting occurs. Hence a victim of poisoning should always be placed in the recovery position (but not when the victim has suffered anaphylactic shock).

Recovery position: Place the victim on his or her front with one leg bent and the arm on that side raised. Turn the head to the same side. Tilt the head back so that the chin juts forward. Cover the person with a blanket or clothing for warmth.

Box 6

InductionofVomiting

1. Sometimes it may be necessary to make a person vomit in order to expel the drug from the stomach.
2. It must be done only if specifically advised. It can be done in the following ways:

* By tickling the back of the victim's throat.
* By giving the victim plenty of salt water (4 tablespoonfuls of salt to each tumbler of water).
* By giving the victim syrup of ipecac, the dose of which should be as follows:

Age	Dose
Under 18 months	10 ml
18 months to 12 years	15 ml
Adults	30 ml

3. **DONOT**

* Induce vomiting in an unconscious victim.
* Induce vomiting if the suspected poison is a petroleum product or a corrosive such as stony acid/alkali. (Hint to recognise a corrosive poison: Lips and mouth may show greyish white stains.)

4.**Ensure**

* The victim leans well forward to avoid choking or inhalation of vomit.
* Clear the victim's mouth of vomit or any other foreign material. This can be done by giving the victim some water to rinse his/her mouth and then spit it out (not swallow it).
* Preserve the vomit for detection of poison at the hospital.

Box 7

DilutionofPoison

1. Usually it is advisable not to give anything to the victim by mouth, unless specifically instructed to do so by your doctor. Fluids may hasten absorption of the drug and thus increase the danger.
2. However, sometimes, the doctor may advise you to dilute any poison left in the victims' stomach after vomiting.
3. Dilution of poison can be done in the following ways:
   a) Ask the victim to drink milk.
   b) Ask the victim to drink beaten eggs.
   c)Ask the victim to drink charcoal powder slurry (prepared by dissolving 4 tablespoonfuls of powder in about 400 ml, 2 glassful, of water). Give half a glass to drink every 15 minutes.

Charcoal powder slurry prevents absorption of poisons which are toxic in small amounts. It is quite safe but should not be used in case of poisoning due to acids and alkalis. Burnt bread powder can be used if charcoal powder is not available.

Box 8

ArtificialRespiration

When there is no rise and fall of the chest and you can feel no movement of the exhaled air, it means that the victim is not breathing. Immediately give the victim artificial respiration (mouth to mouth resuscitation) steps include:

1. Lay the victim on his back on a firm surface. Clear the mouth of vomit or any other foreign material that may otherwise block the airways, and remove false teeth.
2. Place one hand under the victim's neck and lift gently to tip the head back and raise his chin while pressing down on his forehead with your other hand. This should allow the mouth to drop open.
3. Pinch the victim's nostrils closed with the fingers of your hand that is placed on his forehead, and use your other hand to grip his chin firmly to keep the mouth open. Take a deep breath seal your mouth over that of the victim and give two quick breaths. Continue to give further breaths every 5 seconds.
4. After each breath, turn to watch the chest falling while you listen for the sound of air leaving the victim's mouth. Continue until medical help arrives or the victim starts breathing on his own.

Box 9

CardiacCompression

If the victim does not start breathing after two breaths of artificial respiration, check the pulse in the neck of the victim. If there is no pulse, start cardiac compression, *if you have been trained in this technique*.

Cardiac compression is used in conjunction with artificial respiration to start a stopped heart beat.

The technique involves putting repeated strong pressure on the centre of the chest with the heels of both hands at a rate of 80 compressions per minute. At every 10 compressions, two breaths should be given using artificial respiration. This sequence must be continued until breathing restarts.

Box 10

HowtoDealwithaFit?

Certain types of drug poisoning may provoke fits. These may occur whether the person is conscious or not. In a fit, the victim usually falls to the ground twitching or making uncontrolled movements of limbs and body. If you have to deal with such a victim of fit, always remember:

* Do not try to hold the victim down.
* Do not put anything into his mouth.
* Try to ensure that the victim does not suffer injury by keeping him away from dangerous objects or furniture.
* Once the fit is over, place the victim in the recovery position. (Box 5).

Box 11

HowtoDealwithanAnaphylacticShock?

Anaphylactic shock occurs as the result of a severe allergic reaction to a drug. It usually occurs within minutes of taking the drug. In an anaphylactic shock, the blood pressure falls drastically and the air-ways may become narrowed. The main symptoms include: pallor, tightness in the chest, breathing difficulty, rash, facial swelling, collapse.

If you have to deal with such a victim, always remember:

* Check if the victim is breathing or not. If breathing has stopped, give artificial respiration (Box 8) immediately.
* Once the victim is breathing normally, lay him down, face upwards with legs raised above the level of the heart to ensure adequate circulation of the blood. Use a footstool, carton or a similar item to support the feet.
* Cover the victim with a blanket or articles of clothing while waiting for medical help. Do not try to give anything to the victim by mouth.

Box 12

ListofHighDangerDrugs

If anyone takes an overdose of any of the following drugs, immediate medical attention must be sought:

Adrenaline	Lithium
Amitryptiline	Lofepramine
Aspirin	Metformin
Atropine	Morphine
Benorylate	Neostigmine
Chloral hydrate	Orphenadrine
Chloroquine	Paracetamol
Chlorpropamide	Pentazocine
Clomipramine	Pethidine
Codeine	Phenelerine
Colchicine	Phenobarbitone
Co-proxamol	Phenylbutazone
Dextromoramide	Phenylpropanolamine
Diamorphine	Primidone
Digoxin	Procyclidine
Disopyramide	Propranolol
Dothiepin	Pyridostigmine
Glibeclamide	Quinidine
Heparin	Quinine
Hydralazine	Theophylline
Imipramine	Timolol
Insulin	Tolbutamide
Isoniazid	Warfarin
Isoprenaline	

Chapter 2
Essential Drugs

The root causes of ill-health in developing (and underdeveloped) countries like India, are malnutrition, lack of clean water and sanitation, and unemployment. With a population of more than 100 crores, India accounts for about 16 per cent of the global population. India is a country where 37% of the population still live below the poverty line and where the proportion of out-of-pocket expenses out of the total expenditure on health in one of the highest in the world; with only 17% of the expenditure contributed by the government (figures from the National Health Policy 2002). In addition our burden of diseases is among the highest in the world (see box on Load of Diseases). Also see box *Anatomy of Health Disaster* by P. Sainath.

Load of Diseases in India

- Tuberculosis: 1/3 of world's cases: 15 million cases. Largest number of multi-drug resistant cases.
- HIV/AIDS. Second highest in the world: 3.5 million persons.
- Acute respiratory diseases: 950,000 deaths per year.
- Acute diarrhea: 19 crores illness episodes per year and an estimated mortality of 1 lakh children per year
- Malaria especially falciparum malaria is a public health problem with an estimated 2-3 million cases per year and a mortality of 20,000 per year.
- Kala-azar is a significant public health problem in certain states and causes.
- Parasitic infections include hookworm infections, which contribute in a major way to iron deficiency anemia, and filariasis.
- Hypertension: 20-40% in urban areas, 12-17% in rural areas.
- Diabetes mellitus: Largest number of diabetics in the world. 4 % of India's population And cause for 1.1 % of all deaths.
- Cardio-vascular disease: 31.7 % of all deaths in 2000.
- Cancer: Estimates of age standardised rates of cancer range from 99.0 to 129.6 per 100,000 in males and 104.4 to 154.3 per 100,000 in females. 7 lakh new cases per year and cause for 7.4 % of all deaths in 2000.
- Chronic respiratory diseases: 65 million cases and cause for 2.5 % of all deaths in 2000.
- Anemia: Anemia is a major public health problem in women and children with a prevalence of 74.3 %in children of 6-35 months and a prevalence of 49-56% in women (NFHS 1998/99). Anemia contributes to 1/3 of maternal mortaltiy.
-

(Source: Abdul Ghaffar, K.Srinath Reddy and Monica Singhi: "Burden of Non-Communicable Diseases in South Asia", *BMJ*, No 7443, 3 April 2004)

1. Why We Need Only Essential Drugs?

1.1 Increasing Drug Costs to the User

Nearly 50% of healthcare costs are contributed by expenditure on drugs. NSSO surveys reveal figures of up to 80 percent in rural areas. In a study done for the WHO on treatment costs incurred by patients with TB, it was found that 60% of the costs were contributed by drug costs. With the rise in health care costs the number of persons who do not seek treatment because of economic reasons has risen in both the urban and rural areas (NSS 52nd round), which is disturbing. According to a World Bank study,[1] as a result of the costs of a single hospitalization, 35% of people fall below the poverty line.

Anatomy of a Health Disaster

By P Sainath

Janreddy's family survived crop failure. But debts of Rs 300,000 to cover health costs have nearly destroyed them. Loans taken to cover health costs have been a major contributor to the debt-suicide cycle in Andhra Pradesh

Janreddy sat wracked with pain, a picture of ill health. "Why isn't this man on his way to hospital," we asked the neighbours crowding around his bed. "Well," they said nervously, "we just brought him home from one. He was there for days. This family has already lost all its money on hospitals."

Janreddy died hours after we met him. His daughter-in-law, who became a bonded labourer to keep the family afloat, will remain one till debts of Rs 500,000 are paid off. Over Rs 300,000 of that was incurred on medical costs. His wife, who donated one kidney to her son -- both of his had collapsed -- does any work she can find. The son, Narsi Reddy, confined to the house, has to drink only the purest water in a place where there is none. His medicines cost around Rs 1,000 a month.

The huge medical bills of this family of six were incurred despite the son getting free operations at the Osmania Government Hospital in Hyderabad. They had first gone to private hospitals for check-ups, a biopsy and other tasks. As the costs mounted they sold off land and cattle to meet them. That Narsi Reddy had sunk four borewells didn't help. All of them failed. Crisis on their four-acre farm in Chelliagudam village of Nalgonda district saw Janreddy's health also cave in. "They might just have survived the crop failure," say the neighbours, "but their medical costs destroyed them."

Health spending is amongst the fastest growing components of rural family debt. More so in Andhra Pradesh. For years, the state boosted the private sector in health, promoted corporate hospitals and pioneered the 'user fees' system in government ones.

"The Chandrababu Naidu government dismantled the public health system," says M Geyanand, a leading doctor from Anantapur district. Dr Geyanand is also state president of the Jana Vignyana Vedika (JVV), a body that aims to promote popular science and the scientific temper. "Ninety per cent of patients who go to public hospitals are poor. When that system fails them, they turn to private ones at a huge price. Health costs often count for as much as 20-25% of the total expenditures of such households. And a single medical emergency can ruin them."

A common thread running through the farmers' suicides plaguing the state has been very high medical spending. Just five households affected by such deaths had health costs totalling around Rs 400,000. All of them farming families who held between half-an-acre and three acres of land (some of that mortgaged). Janreddy's family has not seen a suicide. But it fits this profile rather well.

As do countless other poor households. Even last year, we ran into a farmer who had attempted suicide in the Nallamada mandal of Anantapur district. His friends managed to get him to a hospital just in time.

The rescued farmer abused his saviours. The reason: The four-day stay and treatment in hospital cost Rs 45,000. "I tried to commit suicide because I could not pay debts of Rs 150,000," he said bitterly. "Now I owe even more."

Many of those who succeeded in taking their lives in 2004 had huge medical bills. P Hanumantha Reddy's family in Nizamabad district owes Rs 200,000. The survivors of A Narasimhalu in Medak have to rustle up Rs 70,000 plus interest. The tab for K Shivarajaiah's family in the same district is Rs 50,000. All this was money borrowed at absurd rates of interest.

"There is a link between the suicides and the crisis of health in Andhra," says Dr Geyanand. "The collapse of the public health system is crucial. In any poor village, you can see people dying of diseases that should not kill them. Malaria is just one example. For years now, all their support systems have been slashed. The costs are so high, they run out of money halfway through treatment. Those who fall ill are selling land, gold, cattle and other assets to pay medical bills. They also take loans they can never repay."

In the past decade, the little access the poor had to health sharply declined. So Gunala Kumar discovered when he had to fork out Rs 40,000 in medical costs to private hospitals in Medak. That remains a big chunk in his total debt of over Rs 200,000. A debt that caused him to take his own life in Meerdoddi village this month. Like his father who committed suicide last year.

"Maybe it is better to die," says Yekalapu Husein of Shabuddlapur in Nalgonda. "How will we pay the fees they ask us to at these hospitals?" A toddy-tapper who suffered a fall from a tree while at work, Husein has run up huge bills himself. Then came his malnourished wife's illness. His 'medical debt' now stands at Rs 200,000. "Even if we get free care at Osmania Hospital," he laughs, "we do not have money for the bus fare to Hyderabad and back."

In Gedavalli village in the same district, the local rural medical practitioner sold all his land to pay his own treatment costs of Rs 400,000 at a corporate hospital in Hyderabad.

In the years these dramas unfolded, public hospitals were starved of funds, medicines and drugs. Given Rs 600 crore by the World Bank for public health, the Naidu government spent this mostly on buildings. Very few doctors or nurses were recruited. The buildings now show decay for lack of maintenance. Naidu also authored a government 'tie-up' with corporate bodies. Under this, employees of the state went to corporate, not public hospitals. The government reimbursed their costs. This meant a windfall for those hospitals. It also meant many scams in the shape of inflated reimbursement bills. Meanwhile, health institutions in the public sphere suffered.

"The introduction of 'user fees' made health even less accessible to the poor," says a senior IAS officer. The fees have since been withdrawn by the new state government. Also dumped was an idea of handing over some super-specialty departments of public hospitals to 'private management'. That is, to corporate hospitals.

The damage, though, has been done. The medical costs of those who preferred death to debt still plague the living. We pass Janreddy's wife at the bus stand, looking for any 'coolie work' she can find. There are, after all, bills to be paid.

(*P Sainath is Rural Affairs Editor of* The Hindu. *He received the A H Boerma Award, in 2001, for his contributions to the development debate in the Indian media.)*

This article originally appeared in The Hindu*, July 1, 2004*

1.2 Increasing Drug Resistance

A problem, which has complicated the control and treatment of infectious and communicable diseases in India, is the increasing problem of drug resistance in common infections and diseases of public health importance. Drug resistance has become increasingly frequent: chloroquine-resistant falciparum malaria, multi-drug resistant TB (new strains resistant to both INH and Rifampicin), new typhoid strains resistant not only to chloramphenicol but also increasingly to quinolones. The latter results in a dramatic escalation

of cost, and requires the use of 3rd generation cephalosporins.[2]

Earlier acute respiratory infections were responsive to the effect of co-trimoxazole, which is an inexpensive drug. Now resistance to co-trimoxazole is being reported increasingly necessitating the use of other drugs for acute bacterial infections in children.

Urinary tract infections are one of the common causes of fever in women. E.Coli, which causes the majority of these infections, has also shown disturbing levels of resistance, first to co-trimoxazole, and now to quinolones and even to cephalosporins.

The problem of drug resistance in common infectious diseases has to be factored in any pharma-related policy in India. Repeated and improper use of antibiotics are primary causes of the increase in drug-resistant bacteria. Misuse of antibiotics endangers the usefulness of essential drugs. Decreasing inappropriate antibiotic use is the best way to control resistance. And more importantly, making unscientific combinations of antibiotics, itself the result of a lack of essentials-only policy, increases the possibility of drug resistance.[3]

1.3 Poverty amidst Plenty?

The situation of medicine availability in India is therefore one of poverty and ill-health amidst adequacy if not plenty. We have a doctor to population ratio almost as good as the US; we have one of the developing world's most flourishing pharmaceutical industries but yet the most common and useful drugs are not easily available, or if available they are unaffordable. Our public sector facilities are very inadequately stocked with essential medicines. (See also Annexure 2: *Access to Medicines: How India Stands Globally?*)

How many drug units are there and how many formulations are made in India? As against the frequently quoted figure of about 20,000 manufacturing units, the actual number of drug manufacturing licenses issued was (numbers in parentheses): bulk drugs (1333), formulations (4534), large volume parenterals (134), and vaccines (56). The total number of manufacturing units engaged in the production of bulk drugs and formulations is not more than 5877. Besides there are 199 medical devices units, 638 surgical dressings and 272 disinfectant units, 4645 loan licences and 318 repacking units, 1806 blood banks, 2228 cosmetics units and 287other units not covered in the above categories.[4] According to the Director, National Pharmaceutical Pricing Authority of the Government of India (NPPA), the number of APIs (Active Pharmaceutical Ingredients) used is 550, APIs manufactured is 400, formulations marketed are 20,000 under 8000 brand names.[5] The NPPA monitors 20,000 formulations and according to its figures, 56 percent of these formulations available are based on a single ingredient bulk drug, 20 percent on 2 bulk drugs, 8 percent on 3 bulk drugs, 4 percent on 4 bulk drugs, 2.5 percent on 5 bulk drugs and 9.5 percent on 5 or more bulk drugs.

If we examine the list of top 300 brands (as per ORG-Nielsen Oct 2003), we find that only 115 brands are of drugs that are mentioned in the National List of Essential Medicines (NLEM) 2003, that is, only 38% of brands of the top-selling ones are of drugs mentioned in the NLEM, the other 62% are of drugs which do not find mention in the NLEM. Among the latter 62% are brands that comprise drugs that are higher priced alternatives without a clear therapeutic advantage, and many drugs that are unnecessary, irrational and even hazardous.

The number of drugs represented by these 115 brands is only 68.

That means the majority of the top selling brands are of drugs which are outside the National List of Essential Medicines, which means that the majority of the drugs which are the most cost-effective for the treatment of priority health needs of the people are not the ones that are selling the most.

A dramatic illustration of the lack of public health relevance of these top-selling preparations is the case of preparations for iron deficiency anemia, which is one of India's most prevalent public health problems.

There is not a single preparation in the top 300, which has the ingredients for an anemia preparation as mentioned in the National List of Essential Medicines.

It is paradoxical that while essential and life-saving drugs are in short supply, more and more drugs which are therapeutically ineffective, irrational and even dangerous, are being produced with absolute disregard to the country's health needs. The problem becomes more acute in developing countries where resources for the purchase of drugs are scarce.

2. Why an Essential Medicines List?

The proliferation of drugs (medicines) and brands creates further confusion even as it is necessary to ensure policies that conserve the country's resources for only useful drugs. Hence there is a need to select essential drugs from those available in the market, many of them being unnecessary.

It is with this in view, the World Health Organization (WHO) promoted the concept of essential drugs. According to the WHO: "Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility."[6]

In 1977, a WHO Expert Committee compiled a list of essential drugs. The WHO list is a model which developing countries can use to make their own selection of essential drugs which were considered "basic, necessary and indispensable to the health needs of the population." They are to be identified by their generic names. The first Model List of Essential Drugs of 1977 identified 208 individual drugs that together could provide safe, effective treatment for the majority of communicable and non-communicable diseases. The 14th Model List of Essential Medicines of March 2005 contains 306 individual medicines in 405 formulations.

Basically, an essential drugs policy means the availability of a minimum number of rational drugs that will satisfy the health care needs of the majority of the people. The key elements in the concept of essential drugs are that they be rational, scientifically proven, therapeutically effective, safe for use, economical and readily available in the country.

The criteria for the selection of the essential drugs (see also box below on *Selection Criteria*) depend on such factors as: prevalent disease patterns, available treatment facilities, training of existing health personnel, financial resources, and the genetic, demographic and environmental factors that influence the state of health and illness in a particular country. They should have gone through adequate clinical tests and found to be safe and effective. Another significant factor is its affordable price and easy availability.

Selection Criteria

Which treatment is recommended and which medicines are selected depend on many factors, such as the pattern of prevalent diseases, treatment facilities, the training and experience of available personnel, financial resources, and genetic, demographic and environmental factors. The following criteria are used by the WHO Expert Committee on the Selection and Use of Essential Medicines:

* Only medicines for which sound and adequate evidence of efficacy and safety in a variety of settings is available should be selected.

* Relative cost-effectiveness is a major consideration for choosing medicines within the same therapeutic category.

* In comparisons between medicines, the total cost of the treatment, not only the unit cost of the medicine, must be considered, and be compared with its efficacy.

* In some cases, the choice may also be influenced by other factors such as pharmacokinetic properties or by local considerations such as the availability of facilities for manufacture or storage.

* Each medicine selected must be available in a form in which adequate quality, including bioavailability, can be ensured; its stability under the anticipated conditions of storage and use must be determined.

* Most essential medicines should be formulated as single compounds.

* Fixed dose combination products are selected only when the combination has a proven advantage in therapeutic effect, safety, adherence or in decreasing the emergence of drug resistance in malaria, tuberculosis and HIV/AIDS.

(Source: *WHO EDM Library*)

An essential drugs list may vary from country to country depending on the above factors. The selection of essential drugs is a continuous process of evaluating the current health needs of the country. The WHO list serves as a model list for adoption in a national health policy. It is revised and updated periodically. (See also Annexure 3 for a sample of country experiences.)

A successful essential drugs programme would:

- Reduce the number of drugs to be produced and available in the market
- Improve the quality of drug management, drug information, and monitoring and utilization
- Reduce the cost to the consumer and to the country as a whole.

2.1 Advantages of an Essential Drugs List

The advantages of adopting an Essential Medicines List are mainly four-fold. They are: medical, social, economic and administrative.

Medical Advantages

* It is medically, therapeutically and scientifically sound, and it ensures rational use of drugs.
* It limits the use of irrational and hazardous drugs and decreases the risks of iatrogenesis (drug- and doctor-induced disease).
* It improves the possibility of monitoring adverse drug reactions in patients.

Economic Advantages

* It is economically beneficial to the nation because it prevents wastage of scarce resources on non-essential drugs.
* The economies of scale achieved in the larger production of priority drugs brings down their prices.
* It curtails the aggressive marketing of non-essential formulations.
* It is economically beneficial to the patient because it prevents wastage on irrational and non-essential drugs.

Social Advantages

* It responds to the real health needs of the people.
* It facilitates the dissemination of correct information about the drugs to health personnel, medical practitioners and consumers in general.
* It helps us prioritise the most urgent needs of the people for essential health care.

Administrative Advantages

* It makes quality control easier because of the limited number of drugs to be monitored.
* It facilitates the streamlining of production, storage and distribution of drugs, because of the smaller number of drugs involved.
* It helps in the clear identification of the drugs.
* It facilitates the fixing of prices as well as the revision/withdrawal of duties, sales tax, etc.

An essential drugs programme is to be implemented as part of a rational drug policy. Its implementation depends on the political will of all governments without which drug marketing will continue uncontrolled with aggressive promotion of useless, irrational, dangerous or expensive drugs; low cost, essential drugs will continue to be in short supply; and information on useful, essential drugs will remain dangerously inadequate.

2.2 Essential Lists in Countries

The WHO's Action Programme on Essential Drugs recommends about 306 drugs in its March 2005 list -- to meet most of the health care needs of any developing country. As of 2002, 156 countries have had a national list of essential drugs, of which 81% have been updated in the previous 5 years.

In 1972, the Sri Lankan government selected 600 essential drugs. In 1977, Afghanistan reduced the number of drugs from over 2000 to 400 in private as well as public sector and allowed the sale of drugs only by their generic names. Nepal in 1986 chose 260 drugs for the national level with approved list of essential drugs for various levels. Mozambique chose 343 drugs in 1980, Iran selected 600 in 1980, and Kenya a maximum of

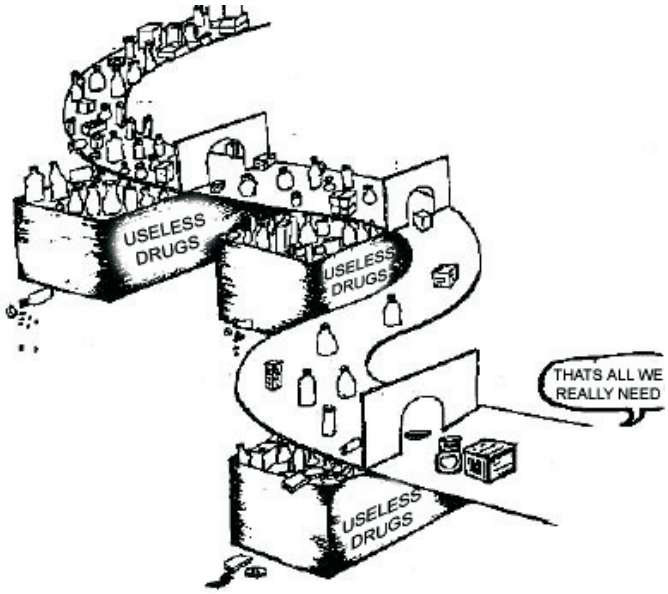
200 drugs. Bangladesh issued a drug ordinance in 1982 allowing only 150 drugs (see Annexure 1 for criteria used in Bangladesh to weed out non-essential drugs). Norway and the Scandinavian countries have also implemented the essential drugs list. Other countries which have taken the lead include: Belarus, 1995 (250 essential drugs); Georgia, 1995; Maldives, 1995 (532 drugs by generic name); Turkey, 1995 (382 drugs) and South Africa which had an essential drugs list in 24 therapeutic groups for primary health care (1996) with standard treatment guidelines. The Hathi Committee which was appointed in 1977 by the Government of India to study the drug industry in India recommended that greater emphasis be laid on the production of 117 identified essential drugs and recommended abolishing the use of brand names in a phased manner. However these recommendations have been ignored by the Government of India.

The Government of India's Ministry of Health and Family Welfare had come out with an essential drug list in 1996 and again in 2003. The latter called National List of Essential Medicines (NLEM 2003) consists of about 350 drugs. The NLEM has to be seen in the context of the National Health Policy (2002) and the Pharmaceutical Policy (2002). Both the 1996 and the 2003 lists have been hanging out in the air without any directions to public health facilities in India as to how to use the same. In the meanwhile, many State Governments, notably Tamil Nadu, Delhi and Rajasthan, have implemented the list actively by using them in their bulk procurement exercises for all the Government health facilities in their States. Considerable savings have been reported (see later in the chapter) by the adoption of such lists.

The Report of the Government of India "Task Force to Explore Options other than Price Control for Achieving the Objective of Making Available Life-saving Drugs at Reasonable Prices" (Sep 2005) has recommended that all drugs in the National List of Essential Medicines (NLEM) 2003 should form the basis of drugs for price control/monitoring.

Despite the WHO recommendations for the use of essential drugs list and implementation of the programme and the Hathi Committee report calling for urgent measures to improve the Indian drug situation, the drug formulation market in India remains skewed. This is because, as already mentioned, many non-essential drugs and drug combinations, that do not find mention in any standard pharmacology textbook, are licensed for manufacture in India and thus find their way in the Indian market (see Chapter 3 for more discussion on this issue).

Essential drug lists have however not been successfully implemented in most countries due to pressure from transnational companies and other vested interests. WHO's own double standards are another major reason the essential drugs concept has not got the importance that it deserves (See box *Failure to Speak Out*). Nevertheless WHO's Essential Medicines Division claims that more than 150 countries have essential drug lists even as the concept itself had its silver jubilee in 2002.



Source: C.Sathyamala et al. *Taking Sides: The Choices before the Health Worker.* 1986

Perceived Problems with Updating and Dissemination of the WHO Model List

- Range of diseases covered by the Model List is not clear
- Discrepancies between Model List and treatment guidelines
- Selection is more consensus-based than evidence-based
- Use of data on cost and cost-effectiveness unclear
- Reasons for selection insufficiently recorded
- Drugs included without pharmacopoeal standard or supplier
- Official report comes out too late, and in English only

Source: <www.who.int/medicines/library/pptpres/edconcept_modellist.ppt>

Failure to Speak Out

Why is WHO not more consistently open in its support of the selection of essential drugs, the international drug marketing code and national drug policies?

The USA has consistently opposed WHO's policies on drugs in the interest of its own Transnational Corporations (TNCs). Recently it changed its position on the development of national drug policies in relation to Third World countries only. During the 45th World Health Assembly in Geneva in 1992, the US delegation opposed an amendment to a policy statement on essential drugs, which proposed that all member states should take steps to implement the concept of essential drugs in their national policies in order to expand access and affordability. The US delegation forced the house to add the words 'where appropriate' to the amendment to make sure that such resolutions have selective application only.

What prevents WHO from speaking its mind openly? Is it because of the USA's reluctance to endorse its policies? Is it that the withdrawal of the USA from UNESCO arouses fear that it will likewise withdraw from WHO if the organisation takes definitive action on drugs without its concurrence? This would be a major financial blow as the USA contributes almost 25 per cent of the total WHO budget (another 20 per cent being contributed by Germany and Japan together).

There are other possible explanations. WHO's staff consists primarily of doctors, from both Third World and industrialised countries, who are skilled in the scientific diagnosis and treatment of diseases but rarely show concern for social and environmental factors. Most of them fail to appreciate that a disease such as tuberculosis is an indicator of social inequality or that malnutrition and insanitary conditions contribute significantly to the incidence of the most common diseases of the Third World. They are unwilling to analyse these problems from a political or economic point of view.

WHO always takes an apolitical, neutral stand and, in adherence to its principle of non-interference, refrains from mentioning colonialism, neo-colonialism and imperialism, all of which have played a significant role in the causation and spread of diseases among the exploited and oppressed people of the world. As the *British Medical Journal* has pointed out, 'WHO should be doing more to tackle the root cause of most diseases - poverty - and doing more to improve infrastructure of health care in the developing world'.

Such action as WHO has taken on drugs is typical of the technological approach to health problems with which medical officers working for WHO feel familiar and comfortable. Doctors understand drugs in so far as they know about prescription and usage, efficacy and quality, but they do not apply their minds to the problems of how drugs reach the people who need them most. They do not realise that the class character and political will of the government determine the affordability and provision of essential drugs.

Nowhere in its documents does WHO clearly state that its essential drugs list is for both the private and the public sector. Moreover, WHO has not even highlighted the views of its own experts on this subject and

allowed these to gain public attention. By the end of the 1980s the drug industry had come to accept, albeit reluctantly, the essential drugs strategy for the public or welfare sector but insisted that the private sector should be left to market forces and to the clinical wisdom of doctors. This provoked a sharp response from Professor Olikoye Ransome-Kuti, former health minister of Nigeria: 'Drugs are meant for diseases not sectors. If you can demonstrate to me that the diseases affecting people in the private sector are different to those affecting people in the public sector we shall adjust the list accordingly'.

Although Professor Ransome-Kuti was the president of WHO's Executive Board for many years, he did not succeed in incorporating his arguments into WHO's essential drugs policy statements. Dr. Mahler and his successor, Dr. Hiroshi Nakajima, made the rules. Whether this was done in ignorance or in collusion with the industry needs to be investigated before essential drugs policies can be fully implemented in Third World countries. In the absence of a clear declaration by WHO, plenty of room exists for easy penetration of ineffective and harmful drugs, first into the private sector and then into the public hospitals and the primary health care (PHC) sector. In reality, inessential drugs eat up a large proportion of the PHC sector drug budget.

WHO is known for its fixation on medical technology - vaccines, drugs and doctors - (and) its unwillingness to grapple with the practicalities of delivering health care. It does not state clearly that disease is not merely the consequence of poor health services and that the provision of primary health care alone does not bring better health. To break the chain responsible for diseases among the poor requires a political decision to act. To publish materials and then not to distribute them widely; to produce documents on drug policy but not to defend them actively, as in the case of Bangladesh's National Drug Policy: these contradictions reflect a political decision not to act. They are also examples of WHO's double standards and its dubious role. Moreover, the organisation escapes the moderating influence of public accountability and scrutiny from the international press.

Source: Chowdhury, Zafarullah. The Politics of Essential Drugs. *New Delhi, 1995, Vistaar Publications, pp.137-139.*

3. Generic/Brand Names, Innovator Products and Generics

If done appropriately, condition branding has numerous benefits, the greatest of which is how it creates consensus internally and externally. Such consensus serves to keep brand managers and the clinical community focused on a single story with a lock-and-key, problem/ solution structure. Internally, the activity fosters motivation and momentum, maximizing the product investment by initiating comprehensive marketing efforts early in the process. The product can better own customer perceptions about evolving/ existing disease states, define new patient segments with currently unmet needs and drive attitudes about new scientific modalities that promise greater treatment benefits.

- Vince Parry. "The Art of Branding a Condition." *M &M*, May 2003

Drugs need to be sold only by generic names and not by brand or trade names contrary to what marketing consultants like the one quoted above advocate - in what is considered a "classic" article in branding in pharma industry. We are dealing with human lives here and it is dangerous to manipulate perceptions and manufacture consent.

Paracetamol is a generic or International Nonproprietary Name (INN) name while Crocin is the brand name (that is a proprietary trade name) for the same drug. Like Crocin, manufacturers market paracetamol under different brand (that is, proprietary trade) names. Another example is that of frusemide ($C_{12}H_{11}C_1N_2O_5S$), its chemical name is 4-chloro-N-furfuryl-S-sulphamoylanthranilic acid, its INN is furosemide, and a brand (or proprietary trade) name is Lasix (for more on INN, see below).

3.1 What is an INN?

An **International Nonproprietary Name** (**INN**) is the official nonproprietary or **generic name** given to a pharmaceutical substance, as designated by the World Health Organization. The plethora of named proprietary preparations containing a given substance can lead to confusion about the identity of the active ingredient. INNs facilitate communication by providing a standard name for each substance. A similar role is played in chemistry by IUPAC names, however these are less suited to common usage, being typically very long and unwieldy.

WhatistheuseofanINN?

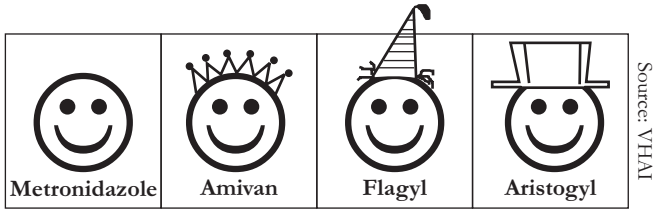
Nonproprietary names are intended for use in pharmacopoeias, labeling, product information, advertising and other promotional material, drug regulation and scientific literature, and as a basis for product names, e.g., for generics.

Some countries have defined the minimum size of characters in which the generic nonproprietary name must be printed under the trademark labeling and advertising laws. In several countries, the generic name must appear prominently in type at least half the size of that used for the proprietary or brand name. In some countries it has to appear larger than the trademark name. Certain countries have even gone so far as to abolish trademarks within the public sector.

There is a school of thought especially sanctified by resolution 46.19 of the 46th World Health Assembly that brand names cannot be derived from the INN and, in particular, must not include their common stems. Some feel the selection of further names within a series will be seriously hindered by the use of a common stem in a brand name.

However proponents of the counter-argument point out that use of common stems will be a half way house to the ultimate rational, scientific goal of marketing and identifying drugs by only generic names. Also using brand names that are totally unrelated to the generic name (that is INN) can create only further confusion in a country like India where anarchy prevails in the medicines market, thanks to the tremendous proliferation of brand name drugs in the market, and many of them irrational combination drugs at that. Also using totally unrelated brand names would help only big pharma with marketing clout to induce brand name recall in prescribers and end users.

In fact small-scale and medium-scale companies will have to spend more money that will get reflected in even higher prices and probably eventually wipe them out.



The same with different names

3.2 Advantages of Selling Medicines by Generic Names

Only 60 to 80 drugs are prescribed most of the time, from over 20,000 branded formulations in the country. It is a common practice among doctors to use brand names when prescribing. Prescribers are often influenced by the marketing practices of pharmaceutical companies. Drug companies claim drugs sold under brand names are of better quality than those sold under generic names. This is a myth. Quality depends on the ethics and integrity of the manufacturer, distributors, retailers and the regulatory authorities (for more on this, see the discussion on Chapter 4 on Quality, and also on Lentin Commission).

Use of brand name is an important issue for the profit-oriented drug companies. The Kefauver Committee (87th US Congress Hearing on Monopoly and Anti-trust (Drugs) 1961) reported that innumerable branded products were being sold at prices ten times higher than their generic equivalents. In India, brand names used to be subject to excise duty of about 15 percent, and generics were excise free; now there is a uniform excise.

One of the reasons drug industry, especially the innovator company, is keen on selling by brands, and not under generic names, is to recoup as much profits as possible, even during the post-patent expiry period, taking advantage of brand-recall. These profits are necessary, the industry claims, to meet R & D expenditures. However, as we discuss later in this book, the costs of R & D are debatable. Much R & D spending goes into producing "me-too" drugs - these are slight variations on existing drugs which can then be patented as "new"drugs and sold at high prices. Often these variations are no better than molecular manipulation or a mere addition of other unnecessary ingredients. Also most of the few but real innovations that have taken place are due to public funding rather than corporate risk taking. (See Chapter 7 for more on R &D and pricing of drugs.)

In contrast, consider the following advantages of having a generic names only policy:

* Only generic names are used in medical and pharmacological textbooks and in pharmacy education.
* Only generic names are used in scientific medical journals and WHO publications.
* Use of generic names will ensure production, sale and dispensing of more rational single ingredient drugs.
* It will ensure clarity by giving information about the class of drug and thus avoid confusion arising out of many dissimilar brand names of one drug.
* Quality drugs are cheaper when purchased under their generic names rather than their brand names.
* Use of generic names is a valuable aid to memory as it is easier to remember only selected names than of numerous brand names.
* Use of generic names will make the selection of essential drugs and formulations for a national formulary easier.
* Use of generic names will curtail the heavy promotion of brands and their high cost.
* Use of generic names demystifies medicine for consumers and health personnel.

The box below gives a profile of drug shortages in Satara district of Maharashtra, marked by inadequate drug policies and irrational prescriptions.

We discuss some FAQs (Frequently Asked Questions) on generic medicines below.

Does the term "generic" medicine have a different meaning internationally, especially in the West?

Yes. Internationally, the term "generic" is used to describe so-called copies of innovator or originator

products. They can be marketed under branded or unbranded versions when the patent period (or the period of exclusive marketing rights) of the innovator product expires. A generic medicine thus is the therapeutic equivalent of an originator pharmaceutical product whose patent has expired. It contains the same active substance, is essentially similar to, and is therefore interchangeable with, the originator product. In the US, the term "generic" is thus used for branded formulations of either (a) off-patent products and/or (b) branded (patented) products where USFDA-approved Market Exclusivity Period has expired (usually 5 years or so).

In India, a medicine is called generic when the medicine is sold by its International Nonproprietary Name (INN). It may or may not be under patent in India. Paracetamol is an INN and is a generic name in India while Crocin is a brand name containing paracetamol. Paracetamol sells under many other brand names too in India.

In this book, we try to distinguish and make clear the two different connotations of the word "generic": we use "generic name medicines" to mean medicines marketed in India under their generic (that is INN) names. Increasingly, the Indian media has started referring to these as "generic generics". Internationally, "generic medicines/ drugs" or "generics" would mean drugs out of patent, which may be manufactured and marketed under its INN name or a brand name given by its generic manufacturer.

3.3 What is a Branded Generic?

Again the term "branded generic" has a different meaning in India and in the West.

"Branded generic" is a term coined by pharma companies in India to create a new market segment for a class of known drugs that benefit the pharma trade greatly by high margins. In India, the class of drugs called "branded generics" are in effect the same as branded products (e.g. Crocin, etc.) but not promoted to the medical profession, but sold through retail chemists. Thus Stanhist of Ranbaxy (containing cetrizine)is a branded generic. Ranbaxy sells Stanhist to retailers for Rs. 3 with a printed MRP (maximum retail price) of Rs. 26. Trade margins for retailers can be as high as 1000 percent and more. On the other hand, Alerid of Cipla is a branded product since it is promoted to the medical profession. Trade margins for wholesale and retail are of the order of 10 and 20 percent respectively for brand name drugs like Alerid and in which the company spends a lot on promotion and marketing to the medical profession.

All large Indian companies like Ranbaxy, Cipla, Zydus Cadila, Lupin, Alembic, et al, are involved in the sale of branded generics. These drugs have given the pharmaceutical trade astronomical trade margins. But they have done nothing to lessen the burden on the consumer.[7]

"Branded generics" exist in the US, one of the biggest pharma markets, but the term is understood to denote something slightly different. Marcia Angell (2004) in her book *The Truth about Drug Companies* has this to say:

> … I should mention a new hybrid called "branded generics." Their active ingredients are similar but not identical to those of the brand-name drugs they mimic, so they supposedly do not infringe on patents, but they are said to be similar enough that they don't have to undergo clinical testing. Neither big pharma nor traditional generic companies are happy about the competition from branded generics, and both are mounting legal challenges. Branded generics are priced somewhere between brand-name drugs and true generics, and their market share is growing rapidly. They are likely to become very important in the biotech industry, where there are no traditional generics because it is difficult to show they are equivalent to the originals.

3.4 Do Brand Names Create Confusion?

Yes, definitely - from the point of view of consumers and patients but not according to the manufacturers. Drug companies claim brands aid in better recall. From the point of view of the consumer it is difficult to distinguish between similar sounding names of many brands (see Tables 1 and 2 below and Annexure 4). Brand names help companies with marketing power.

Since India till 2004 did not recognize product patents (for definition of product patents, etc., see Chapter 6), no one was the "owner" of a molecule in India. However a brand is the "property" of the company such as Crocin of GSK. Very few brands (trade names) are actually registered with the trademark registry in Mumbai. Thus unregistered brands can be used by any one.

As per Indian law, registered trade names (also called brands) are the exclusive property of the holder for a particular "class of products" such as medicines, vehicles, pens etc. Such registered trade names can be freely used for other classes such as Crocin for a pen or Maruti for paracetamol.

"A prescription was written for Lona, a brand of the anti-epileptic drug, clonazepam, marketed by Triton Healthcare Private Limited, Chennai. The "patient" was sold Lona, exactly as prescribed, but it contained

WE HAVE SENT A SPECIAL TEAM TO CATCH ALL THE BUTTERFLIES IN THE WORLD. WE ARE GOING TO COME OUT WITH A NEW VARIETY UNDER DIFFERENT BRAND NAMES.
VERY GOOD. CONSUMERS SHOULD HAVE MORE CHOICES!

Source: Vikas Adhyayan Kendra, Mumbai

low sodium salt marketed by Dabur and meant for hypertensives!" (For more, see the original article in Annexure 4, *Right Brands, Wrong Medicines: Dietary Salt Dispensed in Place of Epilepsy Drug*. See Tables[i] 1 and 2 below.[8])

Table 1: Some Look-Alike Brand Name Medicines in India

Brand name	Composition	Manufacturer	Use
A to Z	Multivitamins	Aglowmed	Vitamin supplementation
AZ-1	Azithromycin	Kopran	Antibiotic
AZ	Albendazole	Cure Quick Pharma	Worm infestation
Celib	Celecoxib	Unichem Lab Ltd.	Pain, inflammation.
Celin	Vitamin C	Glaxo Smith Kline	Vitamin C deficiency
Eltocin	Erythromycin	IPCA lab. Ltd.	Antibiotic
Eltroxin	Levothyroxine	Glaxo Smith Kline	Thyroid hormone
Fasigyn	Tinidazole	Pfizer	Amoebiasis
Fasizym	Enzymes	Infar	Pancreatic insufficiency
Glyred	Gliclazide	Novartis	Diabetes mellitus
Glyrep	Metformin	Emcure Pharma	Diabetes mellitus
Orfiz	Oral rehydration salts	Novartis Pharma	Diarrhea and dehydration
Orfix	Cefixime	Orchid	Bacterial infection
Pronim	Nimesulide	Unichem Ltd.	Pain, inflammation
Pronil	Fluoxetine	PIL Pharmacia India Ltd.	Depression
Tobitil	Tenoxicam	Ranbaxy	Pain, inflammation
Tibitol	Ethambutol	PCI	Tuberculosis
Trip	Nortryptiline	Pfizer	Depression
Triz	Cetrizine	Indoco remedies	Allergic disorders
Vizole	Levamisole	M.M.Labs	Worm infestation, Immunomodular
Vinzole	Omeprazole	Vintage Labs	Acid-peptic disease

* Source: *Drugs Today,* April June 2005, *CIMS* April-July 2005, Rataboli etal JPGM op.cit[9], *MIMS India*, June 2005.

A patient with arthritis may end with Vitamin C, a patient with depression may be dispensed an anti-allergic, an obese diabetic given metformin may be given gliclazide instead, as a result of these confusing brand names.

Sometimes the same manufacturer markets drugs which are different but under similar sounding (and similar looking at first glance) brand names.

[i] These tables are courtesy Dr Anurag Bhargava and the source cited.

Table 2: Same Company, Different Products, Similar Sounding Brand Names

Brand name	Composition	Manufacturer	Use
PD- Mox	Amoxicillin	Parenteral	Antibiotic
PD- Rox	Roxithromycin	Parenteral	Antibiotic
Clomine	Clomipramine	PIL	Obsessive compulsive disorder
Clozine	Chlorpromazine	PIL	Schizophrenia
Zyrof	Rofecoxib	Zydus	Anti inflammatory, now withdrawn from the market
Zyrop	Erythropoeitin	Zydus	Anemia of renal failure
Taxim	Cefotaxime	Alkem	Antibiotic for serious infections
Taxim-O	Cefixime	Alkem	Antibiotic

* Source: *Drugs Today* April-June 2005, *CIMS* April-July 2005, Rataboli etal JPGM op.cit., *MIMS India,* June 2005.

We respond to some other FAQs.

Why is it felt in India that medicines marketed under brand names are of better quality than those marketed under only generic names?

There is no justification for this. It is argued they are likely to be of better quality because companies that have invested in building a brand would not compromise with quality. However it is seen that some very well-known drug companies and brands are frequently hauled up for violations of quality (see Chapter 4 for more details). There is no therapeutic difference between a medicine selling under a generic name and an equivalent drug selling under a brand name. The difference is in price, with generics selling normally much cheaper than brand name drugs.

Should endusers and prescribers rely on the quality of medicines marketed under generic names?

There is no reason why one should not rely/trust medicines marketed under generic names - especially if they are made by companies with Schedule M/GMP certification. Schedule M certification is a must post-July 2005 in India although there are still many companies, at the time of publication of this book, who are yet to fulfill Schedule M requirements.

How do I check for quality of medicines be it generic-named medicines or branded ones?

You can go by the manufacturer's reputation, by word of mouth and "impressions" of reputed prescribers. But these are all imprecise and unscientific. Looking at a packing of a drug will only give you some idea. It does not mean a drug which is available in bulk packing, as contrasted to those in strips or blister packing, is necessarily of poor quality. Neither does it mean that a medicine which is very attractive packaged is necessarily of good quality.

The best way to check for quality is through reputed quality control laboratories - reputed for integrity.

Whatarethequalitystandardsandbenchmarks?

The pharmacopoeias of different countries specify recommended quality standards and methods of analysis for selected pharmaceutical products, excipients, and dosage forms. In India it is the Indian Pharmacopoeia (IP).

There are also quality assurance guidelines in the areas of production, testing, and distribution of medicines. These include guidance on: good manufacturing practices; quality assurance for regulatory approval; prequalification of medicines, laboratories, and supply agencies. Quality means safety and efficacy throughout the life of the product.

A good quality drug can become "bad" if it is not stored properly at the user end. Sometimes a wrong diagnosis is made and medicines are prescribed which then naturally would not work.

Is it possible that a drug independently certified for good quality by a reputed quality laboratorywouldstillnotwork?

Yes, it is possible, but unlikely. Some drugs do not work on some cases, for example in some hypertensives, for reasons not well-understood. Some human bodies just reject some drugs, again not well-understood. It is also possible, the micro dosage of a drug has just not got lodged in the overall tablet during manufacture. But statistically the latter has very low probability.

Is it possible for the same drug made by a different (but quality conscious) manufacturer to showuppreviouslyunreportedadversedrugreactions?

Yes, it is possible, and again this is poorly understood. Some of it could be due to "idiosyncratic toxicity": toxicity problems that only show up under a combination of conditions. Because of the role of variations in human drug metabolizing enzymes there may only be subtle (or no) evidence of such problems during pre-clinical safety studies. Such problems are also unlikely to show up in all but the largest clinical trials, but if the side-effects are serious, it can result in product withdrawal.

The science of pharmacogenomics deals with the analysis of the effect of genomics, especially genetic variation (polymorphisms), on drug response. This may help us understand such unexpected behaviour of drugs better.

Isitpossibletozeroinonaparticularexcipientofadrugthatcausedtheadversedrugreaction, sayarash?

In principle yes, but in practice it is a very costly process involving intelligent guess work and is like searching for a needle in a haystack.

What about the quality, safety and efficacy of a generic named medicine marketed under its genericname(thatisINN)?

In India, it is the duty of the Drug Controller of India and the State Drug Authorities to assure and regulate quality of all drugs in the market. Be it drugs marketed under generic names or their branded equivalents, all have to follow the same quality specifications in the pharmacopeia cited on the label (usually Indian Pharmacopoeia).

Isthemarketperceptionofthequalityofagenericnamedrugakindoftradebarrier?

Scientifically, no, and it should not be. However, as medicines become entwined with political and economic clout, it is being seen as a trade barrier. Companies with dominant brand name drugs would insist that their drug is superior to equivalent generic name drugs and are likely to use media to plant stories to mislead the public. Quality standards can become, and have become, trade barriers if you insist on quality specifications that entail sudden large expenditure for a pharma company. This is the reason why many medium- and small-scale companies are not able to comply with Schedule M specifications of the Government of India and have closed down. Likewise, international harmonization of standards, apparently done with good intentions, can often play a similar role. Also definition of "counterfeit drugs"can be a self-serving exercise by those who want to control market shares. (See also "Counterfeit Drugs: Terms of Discourse" in Chapter 4.)

3.4 The Non-Use of Essential Drug Lists

Essential drug lists are not an end in themselves. They are but a means to ensure good health care. Many State Governments in India have developed essential drug lists; indeed the Government of India's Ministry of Health and Family Welfare has produced lists as recently as 2003 (NLEM, available at <http://mohfw.nic.in/>) and earlier in 1996. But they are not implemented. At best they are left in limbo as is the case with the NLEM, this despite the National Health Policy (2002) document having the following paragraph:

> 4.11.1.1 This Policy emphasizes the need for basing treatment regimens, in both the public and private domain, on a limited number of essential drugs of a generic nature. This is a prerequisite for cost-effective public health care. In the public health system, this would be enforced by prohibiting the use of proprietary drugs, except in special circumstances. The list of essential drugs would no doubt have to be reviewed periodically. To encourage the use of only essential drugs in the private sector, the imposition of fiscal disincentives would be resorted to. The production and sale of irrational combinations of drugs would be prohibited through the drug standards statute.

The reasons for non-use of essential drug lists, after formulating them, are many. But the main ones appear to be:

1) Governments do not take the next steps required, legal and political, to mandate procurement and use of medicines for government and public sector procurement systems as per essential drug lists only.

2) Governments do not ban and weed out all drugs not in the essential drug list, especially irrational and unscientific ones. In fact, the market continues to provide incentives for production and sale of irrational and non-essential drugs.

3) Vested interests in medical profession and the lobbies of traders and manufacturers oppose steps suggested above.

4) Doctors continue to prescribe the latest (and costlier) drugs than adhering to the essential drug list.

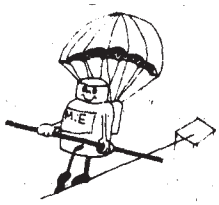
5) A lack of pricing policy that encourages only essential and rational drugs.

Esswntial Drugs Song
(from Nicaragua)

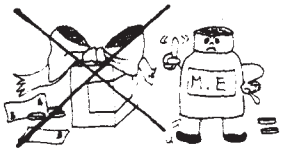
Essental drugs, essential drugs,
few in number, great in worth,
effective, safe and needed

They work to treat,
prevent, and cure
any common illness
Essential drugs, essential drugs...

They are produced
because such drugs
are guaranteed effective
Essential drugs, essential drugs...



All drugs have risks
but with EDs
they're known and understood
Essential drugs, essential drugs...



Their "clothes" aren't smart
just something plain
that's why they cost much less
Essential drugs, essential drugs...

At home and work
demand EDs
and always use them well

Where essential drug lists have been formulated, the lack of one or more of the following may lead to the non-implementation of the concept: standard treatment guidelines, prescription audit, quality checks, transparent and efficient procurement, supply and distribution systems, sufficient budgetary allocations and overall proactive public-health care oriented management culture. Standard Treatment Guidelines, for instance, have to be practised otherwise they remain on paper.

A Study of Drug Shortages in Satara District

Of the more than Rs. 9000/- crores of drugs that are consumed every year in India, it is acknowledged that a substantial part of these drugs are irrational combinations which are also wrongly used. In the Government sector, there is a great deal of shortage of drugs. A study by Phadke, et al. examined the supply and use of drugs in an average district in Maharashtra with the specific objective of studying the amount and the pattern of drug supply to the public and private sector in Satara district, and the shortages in the public sector. The study illustrated the urgent need for implementing a national programme for essential drugs to avoid unnecessary expenditure due to irrational prescribing. The conclusions of the study are probably applicable almost to all districts of India:

Based on socio-economic indicators of development [Centre for Monitoring Indian Economy (CMIE) index], drug supply and OPD attendance in public health facilities, Satara district was chosen as an average district in Maharashtra. Based on socio-economic considerations, the talukas in Satara district were divided into developed, average and drought-prone zones. Three Primary Health Centres (PHCs), one Rural Hospital (RH) from each zone (nine out of 69 PHCs and three out of 10 RHs), one Cottage Hospital (out of two) and the District Civil Hospital were selected to study the amount of each drug indented and supplied to the Government health facilities, shortages, if any, and the dynamics of supply, utilisation and shortages. The total number of drugs and their formulations supplied, were recorded in physical terms as well as their prices to arrive at the drug-expenditure. All these data were re-arranged as per the categories of the WHO essential drugs list.

To study the regularity of availability of drugs, the date of supply and the date of nil stock were recorded for each drug. Depending upon the availability in days, of different drugs, they were grouped into six categories (i) Always Available, (ii) Regularly Available, (ii) Irregular, (iv) Very Irregular, (v) Effectively Not Available, (vi) Never Available.

An estimate of the total sale of drugs in the private sector was made on the basis of informal yet very reliable sources of information.

The overall conclusions of this study were:

1) The drug-supply to the public sector in Satara District was a mere Rs. 5.6 million, as compared to the most minimum, reliable estimate of a drug sale of Rs. 212.8 million in the private sector during 1991-92. The drug supply especially to PHC and RHs suffers from chronic gross shortages and haphazardousness.
2) The overall quality of prescriptions of doctors both in public and private sector is low. There is very high proportion of use of unnecessary, irrational, hazardous drugs and unnecessary injections especially in the private sector. Public sector prescriptions are more rational than private sector prescriptions. Proportion of rational prescriptions increases with educational qualifications.
3) There is very little of proper Continuing Medical Education (CME) of doctors. This along with the influence of the Medical Representatives, increasing prices drugs and competition amongst doctors, influence the prescriptions of doctors in the private sector, whereas in the public sector, the chronic shortage of drugs affects prescriptions, apart from lack of proper CME.
4) Knowledge of PHC-nurses about the drugs they use is satisfactory as regards indications and dosage but quite unsatisfactory as regards precautions and side-effects.
5) Due to irrational prescribing, 69 per cent and 55 per cent of the money spent on prescriptions in the private and public sector respectively, is a waste, with an average of 63 per cent. Projected to the Satara district level, this wastage amounts to Rs.17.7 crores out of the total drug supply of Rs.22 crores.
6) Patients visiting government clinics in Satara district have to buy 15 per cent of the drugs prescribed to them, instead of getting all drugs free.

7) If all the patients coming to the six PHC under study, were to be adequately and rationally treated, there would be a drug-shortfall of Rs. 30525.92 per PHC. This shortfall can be met by a mere 8.42 per cent increase in the annual recurring expenditure of Rs. 0.363 million per PHC.

8) If all the patients in Satara district were to be adequately and rationally treated and if all children and women were to be fully covered in the Mother and Child Health Programme in 1991-92, the drug-expenditure would have been Rs. 20.61 crores, compared to the total drug expenditure of Rs. 21.84 crores in Satara district. It is thus, not lack of resources, but its irrational, wasteful use, which is responsible for the unmet drug needs of the Satara district.

The overall drug situation in Satara district is that of 'Poverty Amidst Plenty' - poor drug supply to the public sector, poor quality of prescriptions, a lot of wastage of the (otherwise) adequate drug expenditure incurred by the people in Satara district.

4. Implementation of Essential Drugs Idea in Two States of India

Atleast two state governments are known to have taken the initiative and implemented the essential drugs concept in India: they are Delhi and Tamil Nadu.[11]

4.1 Tamil Nadu Initiative in Essential Drugs[12]

A major Government initiative was to set up the Tamil Nadu Medical Services Corporation (TNMSC), a Government company, to provide necessary services to Government hospitals. One of the main objectives of the Corporation is to organise an efficient, centralised drug procurement and distribution system. The Corporation has a Board of Directors, with the State's Secretary for Health as an ex-officio Chairman, and a full-time Managing Director.

PromotingtheEssentialDrugsConcept

Under the previous system, hospitals put in requisitions for drugs and then tenders were invited. It was soon evident that the total of 960 drugs procured in this way could be substantially reduced. Many of the drugs were wanted in very small quantities, and central purchasing for such small quantities was uneconomical. Other drugs on the list were deemed non-essential. The Corporation decided to introduce the essential drugs concept and an essential drugs list based on WHO's Model List.

TNMSC's first task was to finalise the list of essential drugs it would procure. A committee of leading professors of medicine and therapeutics (including a WHO representative) was constituted to do this. The Committee held several meetings with drug managers and specialists, and after detailed discussions a final list of 240 generic drugs was agreed. An analysis of these drugs indicated that only about 100 drugs made up 90% of the total value of all 240 drugs. While recognising the scope for further reduction in the list, it was decided not to introduce more cuts in its first year. As services in primary health centres and sub-centre are limited, the Committee decided to standardise the drugs that can be supplied to them. The centres can only requisition drugs outside this list in special circumstances.

The reduction in the existing drugs list meant that the Corporation could procure the drugs it needed with approximately 90 per cent of its drug budget. This left other drugs to be purchased locally by the hospitals

out of the remaining 10 per cent, which TNMSC divided among them. These funds cannot be used to purchase drugs which are on the Corporation's list. After further discussions, the list of drugs which can be procured locally was finalised and circulated to all hospitals. To minimise costs, the possibility of calling for tenders for such drugs was considered. But this would have reduced flexibility, been time consuming and in emergencies hospitals might not have received drugs quickly enough.

In a centralised purchase and distribution system, such as that created in Tamil Nadu, some degree of flexibility for local purchase by medical institutions is essential to meet the needs of all. The system of distributing 10 per cent of the annual budget to hospitals has helped the Corporation counter any criticism that the drugs list is inadequate.

ImprovingDistribution

The main objective of Tamil Nadu's drug management policy is to ensure regular supply and prevent stockouts. Previously when drug companies received an order they sent supplies to the medical institution concerned. One or two companies tended to receive huge orders which they could not meet. Another problem was the considerable delay in paying companies, so that they stopped supplying. It was decided to create a chain of 'godowns', warehouses which stock all drugs. A warehouse for storage and distribution of drugs has been established in each of the State's 23 districts. Drug manufacturers are required to supply the drugs to the warehouse. A distribution schedule has been given to the hospitals, which can take drugs from the store according to that schedule. The drug godowns carry three months' stock, with hospitals permitted to draw a month's supply at a time. The safety stock limit is about one month's requirement, although this depends on the turnover of the particular drug and the lead time for obtaining supplies.

IncreasedAvailability

The Government of Tamil Nadu's innovations in drug procurement and management have improved drug availability in nearly 2000 Government medical institutions throughout the State. There is better budgetary control on drug consumption and medical institutions have become more cost conscious. There has been a significant improvement in the quality and appearance of supplies in the Government sector. The planned computerisation of the entire operation should enable even better inventory management, cost control and improved availability of drugs in hospitals.

For a price comparison see Table 8: A Comparison of Tender Rates and Retail Market Rates in Chapter 7 on Pricing of Drugs as also the TNMSC website[13] where drug prices of successful tender items are available in the public domain this in itself is an innovative and desirable objective.

4.2 Essential Drugs Policy in Delhi State[14]

The cornerstone of the new Drug Policy of Delhi State (1994) is the List of Essential Drugs. The first step taken therefore was to prepare such a list. A Committee for Selection of this List was constituted. This contained clinicians, pharmacologists, microbiologists of the concerned hospitals, other leading experts from outside the Delhi State Hospitals and the Drugs Controller of India, the Drugs Controller and the Director of Health Services of Delhi State. After considerable discussions and after taking into account all points of view this List was prepared and widely circulated.

The list was printed on September 2, 1994 and contains a list of drugs for Out-Patients and a list for In-Patients. The medicines available for the Out-Patients - 177 in number - would be available also for the In-Patients. The total number of drugs for the In-Patients came to 275 drugs. In addition there are fourteen vaccines out of which only seven are available for the Out-Patients. There are twelve solutions for correcting water and electrolyte balance.

Several countries and hospitals have lists of essential drugs but in only a few countries are these lists enforced to introduce changes in drug policy such as was done in Iran and Bangladesh. It was essential therefore to take steps to use the list of essential drugs developed at Delhi. Immediately after the list was distributed to all hospitals they were asked not to procure any drugs outside the list except for 10 per cent of the budget spent on drugs which was decided earlier. Any infringement of this order issued by the Minister of Health and Family Welfare in June 1995 would be looked into carefully. This change from obtaining drugs without any common list to obtaining those only on the list was carried out even before the new procurement system had been introduced. It was so done to convince the prescribers that once a common list had been prepared by them it was important not to prescribe any more drugs outside this list as that would be irrational.

A further List of Drugs to be used at the Primary Health Centre and Dispensary level has also been prepared. This contains seventy-five drugs. Only these seventy-five are being supplied to these primary health centres and dispensaries and they necessarily have to use only these drugs. Standard Treatment Schedules are being prepared for use at this level and deals only with these limited drugs ...

The selection of the Essential List of Drugs is a dynamic process and already, before the second procurement cycle begins meetings have been held to modify the first list as necessary. Some drugs from the first list have been dropped because the committee feels there is no need for these. Others were dropped because these were not available in the market.

The only one change made during the implementation of this programme from what was stated in the Drug Policy Statement was that for one highly specialised hospital in the Delhi State, the quantum of drugs to be purchased outside the list was raised from 10 per cent to 20 per cent in view of their need, in limited quantities, for special drugs for highly sophisticated procedures. Experience in limiting prescribing to the drugs on the list is most satisfactory - drugs not in the list are not obtained and not available at the hospitals.

(For an update on both the above case studies, written around 1996, see reference 5 below and endnote 12.)

References

1. *The Selection of Essential Drugs.* Technical Report Series 615. Geneva: WHO, 1977. as well as the 14th Model List of Essential Medicines at<http://www.who.int/medicines/organization/par/edl/eml.shtml>and the WHO Essential Medicines Library at <http://mednet3.who.int/EMLib/>
2. Huss, Carol, ed. *The Banyan Tree: a Textbook for Holistic Health Practitioners*, Vol.I. Pune: Sahaj/Medical Mission Sisters, 1989.
3. See also Chowdhury, Zafrullah. *The Politics of Essential Drugs*. Vistaar (Sage) Publications, New Delhi, 1995.
4. Phadke, Anant. *Drug Supply and Use: Towards a Rational Drug Policy in India*. New Delhi: Sage Publications, 1998.
5. Roy Chaudhury, Ranjit and Nirmal Kumar Gurbani: *Enhancing Access to Quality Medicines for the Underserved.* Anamaya Publishers, New Delhi, 2004.

6. *Impoverishing the Poor: Pharmaceuticals and Drug Pricing in India.* LOCOST/JSS, Vadodara/Bilaspur, Dec 2004.

7. Some of the FAQs are adapted from European Generic Medicines Association website at <http://www.egagenerics.com/FAQ-generics.htm>

8. World Bank. *India - Raising the Sights: Better Health Systems for India's Poo*r, May 2001

9. National Health Policy (NHP) of India at the MOHFW website <http://mohfw.nic.in/np2002.htm>

10. Pharmaceutical Policy 2002 and previous drug price control policies at <http://www.nppaindia.nic.in/index1.html>.

11. National Essential Medicines List (NEML) 2003 at <http://www.expresspharmapulse.com/nedl.pdf >

12. Approved L1 rates for the supply of Drugs & Medicines for the Period from 01-11-2003 to 31-03-2005 at <http://www.tnmsc.com/system.htm>

13. The Kolkata Declaration of the Jan Swasthya Abhiyan, India, adopted in the National Seminar on Pharmaceutical Policy and Access to Essential Medicines, Kolkata on 16-17 April, 2005 at <http://www.jsa-india.org/issues/drugpolicy/kolkata_declaration.htm> See at the same website "A Critique of the Indian Pharmaceutical Policy" by Amitava Guha.

Annexure1

Criteria for Withdrawal of Irrational and Hazardous Drugs: the Bangladesh Example

Bangladesh used the following 16 criteria to rationalise its drugs in its country in 1982. The criteria resulted in Bangladesh having 150 drugs for tertiary care, 45 drugs for primary health care and 12 drugs for village health care workers. The policy included preparation of a national drugs formulary, price control. These with other measures, most important of which was strong support from the government, have actually resulted in the reduction of drug prices over the last decade. (For a detailed analysis of the policy and subsequent developments, see Chowdhury, Zafarullah. *The Politics of Essential Drugs*, op.cit.)

1. The combination of an antibiotic with another antibiotic, or antibiotics with corticosteroid, or other active substances will be prohibited.

   The manufacture in liquid form of antibiotics harmful to children (e.g. tetracycline) will not be allowed.

2. The combination of analgesics in any form is not allowed as there is no therapeutic advantage and it only increases toxicity, especially in the case of kidney damage. The combination of analgesics with iron, vitamins or alcohol is not allowed.

3. The use of codeine in any combination form is not allowed as it causes addiction.

4. In general, no combination drugs will be used unless there is absolutely no alternative single drug available for treatment or if no alternative single drug is cost-effective for the purpose.

   Certain exceptions will be made in the cases of eye, skin, respiratory and haemorrhoidal preparations, co-trimoxazole, oral rehydration salts, antimalarials, iron-folic (acid), etc., as well as certain vitamin preparations, allowing combinations of more than one active ingredient in one product.

5. Vitamins should be prepared as single ingredient products with the exception of B complex. Members of vitamin B complex, with the exception of B12, may be combined into one product. B12 should always be produced as a single-ingredient injectable product. Other members of B complex may also be produced as a single-ingredient product (e.g. B1, B2, B6, etc). The combining of Vitamins with any other ingredient such as minerals, glycerophosphate, etc. will not be allowed. Vitamins may be produced in tablet, capsule and injectable form only.

   No liquid forms will be permitted because of wastage of financial resources and the tremendous misuse involved. However, the manufacture of paediatric liquid multivitamins (with no B12, E, K and/or minerals) will be allowed in bottles of 15 ml size with droppers. The manufacture of paediatric liquid preparations of single ingredient vitamins will also be allowed in bottles of upto 15 ml with droppers.

6. No cough mixtures, throat lozenges, gripe water, alkalis, etc. should be manufactured or imported as these are of little or no therapeutic value and amount to great wastage of our meagre resources.

7. The sale of tonics, enzyme mixtures/preparations and so-called restorative products flourish on consumer ignorance. Most are habit-forming and, with the exception of pancreatin and lactase, these are of no therapeutic value. Henceforth, local manufacture or importation of such products will be discontinued. However, pancreatin and lactase may be manufactured and/or imported as single-ingredient products.

8. Some drugs are being manufactured with only a slight difference in composition from another product but having similar action. This confuses both patients and doctors. This will not be allowed.

9. Products of doubtful, little or no therapeutic value, and ... sometimes harmful and subject to misuse, will be banned.

10. All prescription chemicals and galenical preparations not included in the latest edition of the British Pharmacopoeia or the British Pharmaceutical Codex will be prohibited.

11. Certain drugs, in spite of known serious side-effects and the possibility of misuse, may be produced in limited quantity for restricted use if the risk:benefit ratio is favourable. These will be prescribed by specialists only.

12. The importing of a drug which is the same as one produced in the country, or a close substitute for it, may not be imported, as a measure of protection for the local industry. However, if local production is far short of need, this condition may be relaxed in some cases.

13. A basic pharmaceutical raw material which is locally manufactured will be given protection by disallowing it or its substitute to be imported if sufficient quantity is available in the country.

14. The role of multinationals in providing medicine for this country is acknowledged with appreciation. In view of the calibre of machinery and technical know-how which lies in their hands

for producing important and innovative drugs for the country, the task of producing antacids and vitamins will be solely with the national companies, leaving the multinationals free to concentrate their efforts and resources on those items not so easily produced by smaller national companies. Multinationals will, however, be allowed to produce injectable vitamins as single-ingredient products.

15. No foreign brands may be manufactured under license in any factory in Bangladesh if the same or similar products are available/manufactured in Bangladesh, as this leads to unnecessarily high prices and payment of royalties. In the light of this policy, all existing licensing agreements should be reviewed.

16. No multinational company without their own factory in Bangladesh will be allowed to market their products after manufacturing them in another factory in Bangladesh on a toll basis.

Annexure2

Access to Medicines: How India Stands Globally?

... Despite the progress made in the last decades, the likelihood of a person having access to essential medicines is still affected greatly by that person's income level. The *World Medicines Situation 2004* found that people in poorer countries were much less likely to have access to these medicines. According to WHO, in 1999, roughly 80 percent of the global population without access to essential medicines was living in low-income countries. This is a disproportionate share of the global burden, given their estimates that low-income countries account for approximately 60 percent of the world's population. In contrast, only 0.3 percent of those lacking access to essential medicines lived in high-income countries, which account collectively for about 15 percent of the world's population. In a global context, that 15 percent of the world's population consumes 91 percent of the medicines produced. Of people living in low-income countries, nearly 40 percent did not have access to essential medicines in 1999 (WHO, 2004a).

Geographically, the lack of access to essential medicines is especially severe and concentrated in Africa and India (Figure 1). In fact, 38 percent of the people without access to essential medicines live in India. Another 15 percent of the people without access live in African countries. Together, India and Africa account for 53 percent of the world's population without access to essential medicines. Although the disease burden and mortality from preventable or curable illness is highest in African countries, pervasive poverty means that the continent's share of the global pharmaceutical market is only slightly more than 1 percent. India's and Africa's inordinate share of the global population without access is not entirely a function of population. India accounts for only 17 percent of the world's population. Similarly, Africa has roughly 10 percent of the world's population. This translates to very high absolute numbers of people without access in these two regions. Sixty-five percent of Indians and 47 percent of Africans lack access to essential medicines (Figure 2), while the equivalent proportion is 14 and 22 percent in Europe and the Americas, respectively …

Figure 1

Distribution by region of people without access to essential medicines, 1999
Source : WHO 2004a

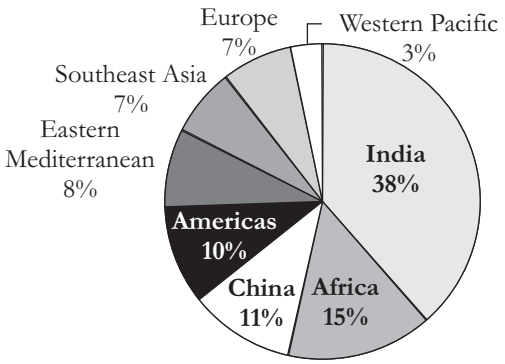
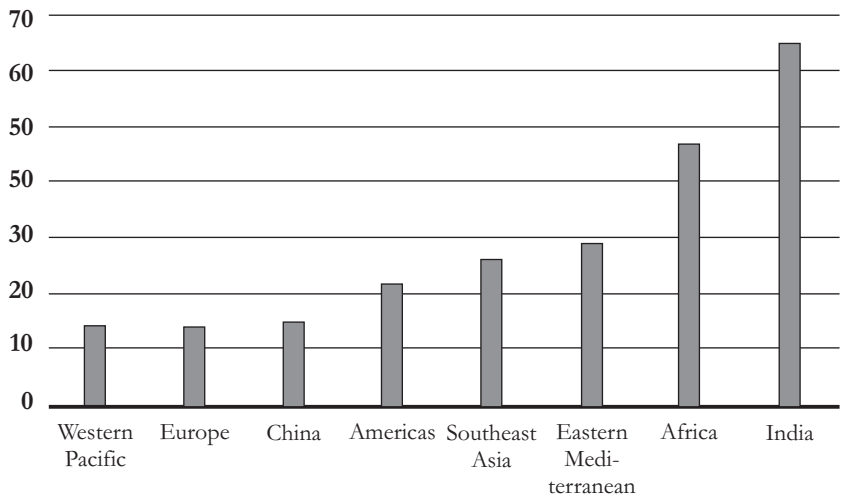


Figure 2

Share of people with out access to by region, 1999
Source : WHO 2004a



Extracted from: *UN Millennium Project. 2005. Prescription for Healthy Development: Increasing Access to Medicines.* Report of the Task Force on HIV/AIDS, Malaria, TB, and Access to Essential Medicines, Working Group on Access to Essential Medicines. Sterling, Va.: Earthscan. pp 27-28. Quoted from *World Medicines Situation 2004,* WHO.

Annexure3

Country Specific Approaches to Updating Essential Drugs and Formulary Lists[15]

Bhutan

A participatory approach was used to update the national essential drugs list (NEDL). A form was developed, and health workers at all levels were invited to propose additions and deletions to the national list. Suggestions were also requested for the level of use for each drug. The proposals were compiled by the essential drugs program coordinator for the National Selection Committee, which made the final decision. The current NEDL consists of 312 drugs and indicates their level of use.

EasternCaribbeanDrugService(ECDS)

The ECDS is a group purchasing service for seven small Caribbean countries. Procurement is limited primarily to the ECDS Regional Core Formulary. Drugs are selected by the ECDS Technical Advisory Subcommittee (TAC), which consists of one member appointed by each participating country (generally the chief medical officer or a comparable ministry appointee) and the central stores managers from each country. The ECDS managing director and assistant managing director are nonvoting members of the TAC. The formulary list is subject to continual review. Changes are based on the evaluation and approval of written requests.

UnitedStatesPublicHealthService(USPHS)

Most drugs for the Oklahoma area of the USPHS are procured centrally, based on a formulary list. Each hospital in the area has a pharmacy and therapeutics committee that reviews drug needs and drug utilization for the hospital and its health centers. The formulary list is revised each year. Hospitals submit suggested additions and deletions to the area pharmacist, who compiles the suggestions. In a representative fashion, the chairpersons from each hospital pharmacy and therapeutics committee then meet at area headquarters to review and decide on the proposed revisions.

Zimbabwe

The first essential drugs list for Zimbabwe (EDLIZ) was produced in 1985. The list contained 581 formulations, 224 of which were allowed at the clinic level. As of 1994, the list had been revised three times and included 409 drugs and vaccines in 592 formulations. The number of formulations available at the clinic level had been decreased to 83, with an additional 259 for district hospitals (with some specialists), and another 154 for specialists' use only. Twenty-four drugs are featured in a supplementary list and can be imported without prior permission from the Ministry of Health for rare life-threatening conditions.

Revisions are carried out by the National Drug and Therapeutics Policy Advisory Committee (NDTPAC), which meets regularly. Its members include a professor from the Department of Pharmacy, University of Zimbabwe (UZ); a general practitioner; the clinical pharmacists, Department of Pharmacy, UZ; a professor from the national teaching hospital; the professor of clinical pharmacology, UZ; and the president of the national pharmacy association (private sector). The secretariat for the NDTPAC includes the director of pharmacy services, Ministry of Health and Child Welfare; the registrar, Drugs Control Council; the controller, Government Medical Stores; and the project coordinator, Zimbabwe Essential Drugs Programme.

The revision process is continual and takes about two years. It actually restarts as soon as a new list is issued. In this way, the merits of all new developments can be discussed and evaluated as soon as they arise. The committee has called on a panel of forty specialists for their views and contributions, and another eighty persons have been asked for comments and opinions. All medical disciplines, as well as pharmacists, buyers, and health economists, are represented, to arrive at the most economical choice with the widest possible coverage for medical conditions prevalent in Zimbabwe.

Annexure4

Right Brands; Wrong Medicines Dietary Salt Dispensed in Place of Epilepsy Drug[16]

Too many medicines in India are being sold under similar, if not exactly identical, brand names. Are patients at risk of consuming drugs not intended for them? As an experiment, a prescription was written for Lona, a brand of antiepilepsy drug clonazepam marketed by Triton Healthcare Private Limited, Chennai. The "patient" was sold Lona, exactly as prescribed, but it contained low sodium salt marketed by Dabur and meant for hypertensives!

There are hundreds of other examples: A to Z contains multivitamins, A-Z has cetrizine while AZ brand is used by at least three different manufacturers for entirely different medicines: azithromycin, albendazole and cetrizine. Imagine the plight of a female pregnant patient who has been prescribed azithromycin for a serious infection being fed on vitamins or cetrizine or still worse albendazole that is prohibited for use during pregnancy.

Even when brand names are not identical, many are deceptively similar. Examples: Sivoxol is a combination of salbutamol, theophylline and ambroxol while Sivozol contains ofloxacin and tinidazole; Tocan contains clindamycin while Tocon is a brand of ketoconazole. A quick glance at the brands of just 300 manufacturers shows that there are more than 20 similar brand names all starting with just one alphabet A such as Adiflox/Adilox, Adlin/Adliv, Alzol/Alzo, etc.

Why does this happen in India? There are many reasons. Firstly, when there are over 17,000 pharmaceutical producers churning out more than 40,000 brands of just 450 or so basic molecules, there is bound to be shortage of unique, distinct brand names. Secondly, producers are keen to use short, easily remembered brand names that give some indication of the ingredient. Alzol was so named because "Al" and "zol" can be identified with albendazole while Alzot is supposed to remind the prescriber of alprazolam Commercial companies are apparently not concerned with the havoc on healthcare caused by such branding.

Under the laws of the land, unlike western countries, drug regulators in India do not have a role in the determination, use and registration of brand names. Drugs Controller General, India (DCGI) is charged with the task of approving new medicines under their generic chemical) names while state level Food and Drug Administrations issue manufacturing licences. None of them is supposed to keep an updated record of brand names used by various companies. In any event, in a federal setup a central authority is needed to monitor the registration of trade names since one state level authority cannot have jurisdiction over another state.

There is no central or state law specific to the use or registration of brand names of medicines. Like other consumer items (telephones, cars, airconditioners), brand names of medicines can be registered with the

Trade Mark Registry. The over-burdened Registrar takes years to approve or reject a trade name application. Its data bank is not updated for months and years. The bigger problem is that it is not compulsory to register trade names of any item in India be it a pen or a pill. In effect it means that if brand name AZ is not registered with the Trade Mark Registry, any number of manufacturers can use it for any number of products. Manufacturers voluntarily register trade names of their products so that others are prevented from using the goodwill and benefit from brand loyalty.

Even when a brand name is registered, it is applicable to one particular class of items. The result: the trade name Lona, even if registered by one company for low sodium salt can be used by another manufacturer for clonazepam since these two items fall under different class of products.

Endnotes

[1] World Bank. *India - Raising the Sights: Better Health Systems for India's Poor*. May 2001

[2] See the website of the Centers for Disease Control and Prevention on antibiotic/antimicrobial resistance at <http://www.cdc.gov/drugresistance/>. Also, *Antibiotic resistance: synthesis of recommendations by expert policy groups*. WHO, 2001 at <www.who.int/entity/drugresistance/Antimicrobial_resistance_recommendations_of_expert_polic.pdf>.

[3] Pharmaceutical Policy 2002 and previous drug price control policies at <http://www.nppaindia.nic.in/index1.html>.

[4] Mashelkar Committee Report (2003). Figures arrived at after soliciting information from each FDA or equivalent of all states of India.

[5] Dr Appaji, Director, NPPA, at a WHO-SEARO workshop on "Medicines in SEA Region", Chennai, Dec 22, 2003. Although NPPA monitors only 8000 brands in 20,000 packs, the actual number of brands in the market would be higher. Even if we assume that on an average each of the 4534 formulators produce only 5 brands, the total number of brands would be about 20,000. Many of the big companies have over 50 brands at a time.

[6] Source: <WHO.://www.who.int/medicines/library/general/PPMedicines/ppm04eng.pdf>

[7] For more discussion on branded generics in India, see Chapter 2, "Anarchy in Retail Prices in India", pp.39 ff in *Impoverishing the Poor: Pharmaceuticals and Drug Pricing in India*. LOCOST/JSS, Vadodara/Bilaspur, Dec 2004.

[8] See "Confusing Brand Names", Letter from Avijit Hazra, *Indian Journal of Pharmacology* 2002; 34: 367-368. A more recent paper is: Rataboli PV, Garg A. Confusing brand names: Nightmare of medical profession. *J Postgrad Med* 2005; 51:13-16

[9] See previous endnote.

[10] Phadke, Anant. *Drug Supply and Use: Towards a Rational Drug Policy in India*. Sage Publications, New Delhi,1998.

[11] For more detailed discussion on pooled procurement experiments in several States of India and the world, please see, Roy Chaudhury, Ranjit and Nirmal Kumar Gurbani: *Enhancing Access to Quality Medicines for the Underserved*. Anamaya +Publishers, New Delhi, 2004. The book also discusses the Bamako Initiative and the Life Line Fluid and Drugs Stores. The latter especially is very relevant for India.

[12] Source: R.Poornalingam. "Drug management in the Government Sector: the Tamil Nadu Model" . WHO's *Essential Drugs Monitor*, Issue no.21, 1996. For a more recent study see "Providing Health Security Through Rational Drug Approach: Evidence from Tamil Nadu" by N. Lalitha, Gujarat Institute of Development Research, Ahmedabad (mimeo, 2004).

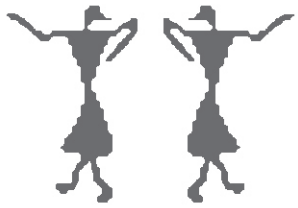
[13] Approved L1 rates for the supply of Drugs & Medicines for the Period from 01-11-2003 to 31-03-2005 at < <http://www.tnmsc.com/system.htm>

[14] Reproduced with thanks from Roy Chaudhury, Roy. "Implementation of a programme of Rational Use of Drugs in Delhi State." International Experience in Rational Use of Drugs, Vol 2, August 1996. For more recent discussion see Roy Chaudhury and Gurbani, op.cit.

[15] Reproduced from *Managing Drug Supply*, MSH, Boston, 1997

[16] Editorial in *MIMS India*, October 2004. Reprinted with kind permission.

Chapter 3
Rationality of Drugs



This is in reference to your appeal, to express our views free to your editorial 'Times for introspection'

1. **Mr. A,** is son of a wealthy father, graduate in law, but couldn't succeed in legal practice, changed his profession to become a commission agent for certain consumer products but didn't find it profitable after few years, married a doctor (main qualification of starting a nursing home), underwent 2 months correspondence course in homeopathy. Now people call him Dr. A, and being highly connected to upper class, got immediate recognition as a 'good doctor' to the extent that he was honored by an internationally renowned voluntary organization along with some post-graduates in medicine and surgery.

2. **Mr. B,** couldn't clear SSC, started supplying medicines to doctors, nursing homes, offering door to door service for a wholesaler, learnt something about symptoms of some diseases and the medicines for their treatment. Seven years after, I find him as a successful doctor, in a remote suburb of a sprawling metropolis.

3. **Dr. C, MBBS** with a post-graduate diploma in a sub-speciality, practising as a general practitioner, gives two i.m. injections to every patient, per visit; one of the injections is invariably dexamethasone, irrespective of diagnosis. He completes writing prescription even before examining the case.

What is the lesson we learn form these representative cases? In our present day medical practice, there is no place for Rationality if this mad crowd, be it a layman, a professional or a politician, is running after material gain, money or power - this may be the answer to your question, why BODHI, a journal dedicated to rational therapy, is not making any progress in a profession where the motive is to make a fortune which is called commercialisation of a service. BODHI is making an attempt to de-commercialise it by disseminating information on rational therapy.

Doctors have forgotten that the practice of medicine is a service, an obligation which he/she has voluntarily accepted and it is no way to make big money, instead it gives him/her a self-satisfaction of being a good Samaritan. Doctors are on the run, away from the goal, envisaged by BODHI.

In a fight between weaker and stronger, the latter wins, unless the weaker has something up his/her sleeve. Your fight against malpractices of pharma companies, especially MNCs, is something like it. A strong support for Rational drug use, by the medical community would be your main weapon against the stronger opponent but the situation is exactly opposite. Doctors feel popularity and profits are in direct proportion to the number of drugs he/she is prescribing and the number of companies he is patronizing. BODHI's fight against these is not welcomed by these doctors!

1. What is Rational Therapy?

Rational drug therapy means the use of drugs, which are efficient, safe, low-cost and easy to administer. It requires that health practitioners have adequate medical knowledge and appropriate skill for correct diagnosis and treatment. They would also be required to have time and concern for their patients.

Rational drug therapy thus is only part of the larger issue of rational treatment - which in turn is a subset of the larger issue of rational health services. Rational health care implies rational diagnosis and treatment. Rational diagnosis means ordering the appropriate amount of procedures, laboratory test, x-ray, etc., not more, not less. Rational treatment also assumes rational behaviour by the patient after a medicine is prescribed, provided he/she can afford it.)

1.1 Rational means also Appropriate

The Oxford English Dictionary defines "rational" as that which is based on reason, which is sensible, sane or moderate. Rational Drug Therapy may be used interchangeably with the concept of *appropriate* therapy, which may be described as ordering the appropriate right medicine for the right/appropriate indication, for the appropriate/right patient at the right time and in the right dose, route and duration, with due consideration of costs.

1.2 An Appropriate Indication for the Use of Drugs should Exist

- An 1-year old with low body weight for age is seen in the OPD, because the parents noticed a pot belly. This is clearly due to undernutrition. The family is poor but the child has not been weaned and given solid foods. Should the child receive advice on feeding or an alcohol-based 'tonic'?
- A chronic smoker comes with cough off and on, especially in the morning. There is no shortness of breath. The clinical examination is normal. Should he receive a cough suppressant, an antibiotic or advice and support for stopping smoking?
- A child comes with viral upper respiratory infection (a rather long and impressive name for a common cold!) with a fever, running nose and a mild cough. Should he receive antibiotic like amoxicillin which would be useful only in bacterial infections, a syrup which has a combination of cough suppressant and cough expectorant (such preparations which are neither fish nor fowl but both abound in the market), or advice that the illness is a mild, self-limiting one, where paracetamol can be used if the fever is significant?
- A 2-year old child comes with diarrhoea with passage of 5-6 loose stools without significant abdominal pain, or any blood. This is again likely to be only viral diarrhoea, which like viral upper respiratory infection is self-limiting. Should he receive oral rehydration solution (even home-made ORS which is rice-based would be appropriate), or a combination of ciprofloxacin (a drug to be avoided in children under 14 years of age) and metronidazole (which is effective only in amoebiasis, giardiasis)?
- A computer professional has low-backache because of long hours of sitting at the desk in a faulty posture on a faulty chair. Should he receive long term pain-killers or advice on posture, exercises and a proper chair which supports the lower back?

- A 24-year old married woman complains of mild nausea in the morning. On enquiry, her periods are overdue by 15 days. Should she receive drugs for nausea or an evaluation for pregnancy?

In each of the above examples, which are very common in our experience, the use of drugs like tonics in under nutrition, cough suppressants in a chronic smoker without advice on smoking cessation, a drug for bacteria like amoxicillin in a viral infection, and use of irrational medications like combinations of antibiotics (ciprofloxacin and metronidazole) or combinations of cough suppressants and cough expectorants, are not indicated at all. The use of such drugs is inappropriate, leading to sub-optimal care, a waste of resources, and endangering the health of the patients. The use of drugs like ORS, and simple antipyretics like paracetamol would however be termed appropriate or rational.

Not only do many conditions require no drugs or very few drugs, but non-drug treatment is an important complementary treatment to treatment with drugs for many common diseases, e.g., weight reduction, smoking cessation, going low on fats in diet, is an important part of the management of diabetes, hypertension, and angina. Similarly eating high fibre diet, drinking lots of fluids, and exercising is important in treating constipation. In many conditions, some form of surgical intervention is indicated from bleeding piles, to gall-stones which are causing symptoms and complications, to cataracts. In all these conditions, drug therapy has no or a very limited place as a primary treatment.

1.3 Appropriate Medicine should be Used: Is it the Right Drug for the Right Patient?

The drug to be used should be efficacious, safe, and cost-effective, and suitable for use in a patient. Which are these drugs that we can rely on? Fortunately, there is broad international and even national consensus on a limited number of essential drugs, which are efficacious, safe and cost-effective. These are the drugs contained in the list of Essential Medicines (this issue has been dealt with in Chapter 2). It is from these lists of essential medicines that we can choose the right drugs for our patients. When we choose drugs from these lists, we are automatically choosing drugs with demonstrated efficacy, safety and cost-effectiveness and practising evidence-based drug therapy.

The list of essential medicines covers the right drugs of choice for treatment of priority disease conditions: be it anemia, asthma, or diabetes, hypertension or epilepsy. How these drugs are to be used is described in textbooks of medicine and pharmacology. Also an increasing number of professional and public health-related organisations bring out Standard Treatment Guidelines for treatment of particular disease conditions. Guidelines from WHO exist for the treatment of TB, leprosy, and other communicable and non-communicable diseases. In India, state level and national level guidelines for treatment of common disease conditions have been compiled, and need to be disseminated and used widely to realize their potential for providing rational, safe and cost-effective care.

Apart from making the correct diagnosis and choosing the right drug from the List of Essential Medicines and Standard Treatment Guidelines, the suitability of the drug for the individual patient has to be assessed before starting the treatment. The drug should not only be right, but be right for our patient. There are a number of factors which need to be taken into account by the prescriber. In fact, all patients can draw the attention of their doctors to these factors while they receive their prescriptions.

There are three things which are absolutely essential to bring to the attention of doctors. The first is any history of a possible reaction to drugs in the past. The second is the possibility of pregnancy in all women of

child-bearing age. Before accepting a prescription for any illness, women should keep this in mind. It is better to rule out pregnancy if monthly periods have been delayed, rather than take a drug unknowingly which can affect the development of a child permanently. The third is any other illness that the patient has and the treatment that he/she is taking for the same.

Age is an important consideration. Some drugs like tetracyclines are not safe in children. In the elderly, the rate of breakdown of drugs is lower so that doses have to be lower and one has to be on the look out for side effects which are more frequent in this group. Pregnancy and lactation affect the choice of drugs in a major way, and women who are pregnant need to exercise particular caution about taking drugs. The individual patient may have allergy to certain commonly used drugs like penicillins and sulfonamides, which have to be therefore avoided. Coexisting illnesses often dictate the choice of drugs, e.g., a patient with hypertension and asthma should not be given a beta-blocker like propranolol which can worsen the asthma, and which can otherwise be used in other patients with hypertension. Patients with diseases of liver and kidney need to be particularly cautious while using drugs, because most drugs need to be modified in doses when these diseases exist, and also because a significant number of drugs can potentially cause side-effects on the liver and kidney and worsen their condition. Even the occupation of the patient has to be taken into account. A drug given for sneezing due to nasal allergy which can cause some drowsiness, would be completely unacceptable in an airline pilot or the driver of a superfast train.

We have discussed in the above paragraphs the selection of drugs from the List of Essential Medicines. What about the drugs which are available in the market and fall outside this list? *Some* of the drugs which are outside this list are of complementary drugs which are to be used in selected patients, under specific situations, in a specific healthcare setup, e.g., certain antibiotics for use in antibiotic resistant infections, or anti-cancer drugs to be used in a hospital setup for use in certain cancers. But a *larger number* of drugs which are outside the List of Essential Medicines are simply more expensive alternatives for essential drugs., e.g., ramipril works on the same principle and to the same extent as enalapril which is an essential medicine for use in hypertension and heart failure, but costs five times more to the patient. In fact a *huge* number of drugs, which do not figure in the List of Essential Medicines are in fact of dubious efficacy, rationale and safety, but are money-spinners for their companies, e.g., most preparations for iron deficiency anemia in this country do not conform to the criteria mentioned in the List of Essential Medicines.

1.4 Drugs have to be Administered in an Appropriate Dose at an Appropriate Interval, through an Appropriate Route for an Appropriate Duration

Sample the following:

- A patient with pneumonia admitted in a private hospital does not improve after 3 days of therapy with a "higher antibiotic." He is receiving Inj. Cefotaxime 1g once a day.
- A woman with high fever, flank pain and discomfort while passing urine, was diagnosed as having an upper urinary tract infection. She was given an antibiotic in the correct dose and dosing interval but for 5 days. Improving initially, she developed recurrence of the same problem two weeks later.
- A patient in a village in Chhattisgarh has had recurrent episodes of malaria over the past 3 months. During each such episode, the patient was administered Inj. Chloroquine 2 ml by an intramuscular injection daily for 3 days.

- A patient suffering from persistent asthma of moderate severity has been on long-term oral medication with salbutamol and oral prednisolone.

Apart from selection of the appropriate drugs it is critical to ensure that the drugs are used in the proper dose, interval, and duration through an appropriate route. This is one area where there is total anarchy in India of which the above is a small sample. The patient with pneumonia received an improper dose. The antibiotic given as 1 dose/day of a drug should have been administered 3 times in a day. The woman with the upper urinary tract infection was given the wrong duration of therapy. She needed to be treated for 14 days to eradicate the infection, yet was treated only for 5 days, which was the reason for the recurrence of the infection. The villager with malaria received the right drug through the wrong route. Chloroquine should have been administered through the oral route and in an appropriate dose of 10 tablets for 3 days. The choice of injections was particularly inappropriate as chloroquine is one drug which is very well absorbed when taken by mouth, and giving the drug by injection led to gross under-dosing as shown below.

Use of Injections of Chloroquine in Uncomplicated Malaria: An Example of Massive Under-Dosing

An adult patient with malaria needs to be a given a total of 1500 mg of chloroquine over 3 days.

One tablet of chloroquine phosphate contains 150 mg of chloroquine. Therefore the appropriate dose in terms of tablets is 10 tablets which is given in the schedule of 4-4-2, in the national antimalaria program (4 tablets on day 1, 4 on day 2, 2 tablets on day 3).

1 ml of chloroquine injection on the other hand contains only 40 mg of chloroquine, which is nearly a quarter of the content of a tablet. Therefore a patient who received 2 ml injection daily for 3 days, received a total of 40x2x3, i.e., 240 mg of choloroquine, which is less than a total 2 tablets of chloroquine and only 1/6 of the dose required for malaria.

Lastly the patient with persistent asthma received an incorrect dosage form of the medication. The treatment of asthma requires not only treatment for relief of spasm with drugs like salbutamol, but also drugs like steroids to prevent spasm from occurring by decreasing the allergy in the airways. However, the long-term use of oral steroids is marked by high risks of side-effects like decreased immunity, diabetes, hypertension and bone disease, and is therefore inappropriate. The beneficial effects of steroids in prevention of attacks of asthma can be gained from taking steroids through inhalation route (through inhalers), which involves taking only a small fraction of the dose taken orally. Steroids taken through inhalers have made their long term use a very safe option, and have revolutionized the treatment of asthma. Even salbutamol should be administered preferably through the inhalation route, as inhaled salbutamol offers the advantage of rapid onset of action, fewer side-effects and flexibility of dosing.

1.5 The Patient should also Receive Appropriate Information

The concept of rational use of medicines also implies that the patients should receive the appropriate information about their disease and the medications prescribed and are appropriately evaluated for the anticipated effects and side-effects. For example a patient with diabetes who is prescribed an oral pill for lowering blood sugar, needs to be explained how to take them, what not to do while taking them (missing meals, going on a fast), the possible side-effects in the form of development of low blood sugar (hypoglycemia), how to recognize the symptoms of low blood sugar, and how to treat the problem of low blood sugar. If the patient does not have this basic information, he may pay for it with his life. There have

been numerous instances when patients have developed low blood sugar, have not responded by taking sugar in some form because of lack of information ,and have ultimately died or lapsed into irreversible coma.

In the current situation of medical practice in India, the patient's Right to Information is given short shrift, and any explanation on the drugs mentioned in the prescription is often perfunctory. This lack of information from doctors is compounded by a lack of information from drug companies.

1.6 Rationality Across Systems

Rationality across systems is a poorly studied issue. Doctors of different systems, and their various protagonists, tend to taken positions: if you are qualified in one system you cannot practise the other system of medicine, unless you are qualified for it also. Some allopaths, that is practitioners of modern, Western medicine, feel that there is no rationality, and therefore no science, in other non-allopathic systems: a position hotly contested and one that soon gets us into issues of privileging one knowledge system over the other. But certainly we can ask for rationality within a particular medical system.

In this book however, we are concerned with rationality within the allopathic (modern, Western medicine) system only. A decision of the Supreme Court (Poonam Verma vs Dr Ashwin Patel in CP No 8856 of 1994) prohibits cross practice: that is no medical practitioner can use medicines that belong to the system in which he is not trained and registered. (See box below: *In Violation of Clear SC Ruling "Quacks" Continue to Conduct Clinical Trials*.)

In Violation of Clear SC Ruling "Quacks" Continue to Conduct Clinical Trials

No practitioner of modern medicine is taught either during the course at the medical college or hospital training about the contents and properties of Pippalyadi Yoga. Yet believe it or not, it is being tested on humans, that too young females, to test if this product has any anti-fertility role.

In Poonam Verma v/s Dr. Ashwin Patel case (CP No. 8856 of 1994), the Supreme Court had outlawed "cross-border" practice and ruled that no medical practitioner will use medicines that do not belong to the system in which he or she is educated and registered. In other words, allopaths are not permitted to use modern medicines.

The apex court had pronounced that a person holding, say MBBS, was a doctor in allopathy but a "quack" in other systems just like any lay person and will be "deemed to be negligent *per se* without any further proof or argument" if found to be administering medicines belonging to other streams.

Pippalyadi Yoga has been developed by the Central Council for Research in Ayurveda and Siddha and claims to contain *Pippali, Vidanga* and *Tankana*. These substances are strange words for medical practitioners because they do not find any mention in the standard textbooks of pharmacology.

Strangely, the unauthorized and illegal clinical trials are taking place at the All India Institute of Medical Sciences (AIIMS), New Delhi; Post Graduate Institute (PGI), Chandigarh; JIPMER, Pondicherry and King Edward Memorial Hospital, Mumbai, all managed by the government. Thus state-run institutions are violating Supreme Court orders.

Because of their prescription powers, allopathic doctors are bombarded with promotional material on Ayurvedic products even though it is unethical and illegal. Since doctors demand evidence of safety and efficacy, some manufacturers of Ayurvedic medicines go to the extent of sponsoring clinical trials of their products in medical

colleges where unwittingly investigators are roped in for illegal trials.

In the past year alone, just two companies have conducted over a dozen clinical trials of Ayurvedic products at medical colleges in violation of Supreme Court ruling. Some examples:

- Safety and efficacy of branded Septilin by Dr. Bharat J. Parmar at Department of Paedaitrics, B. J. Medical College, Ahmedabad.
- Safety and efficacy of branded Ophthacare by Dr. Ulka Srivastava, Professor in Ophthalmology, M. G. M. Medical College, Indore.
- Safety and efficacy of branded Himcospaz by Dr. Shakuntala Prabhu, Associate Professor at Bai Jerbai Wadia Hospital for Children, Mumbai.
- Effect of branded Calcurosin in the management of urolithiasis by Dr. Lokesh Upadhyay at Institute of Medical Sciences, Varanasi.
- Safety and efficacy of branded Diabecon in diabetes by Dr. K. R. Kohli at R. A. Podar Medical College, Mumbai.

Unlike allopathic molecules, all these trials are conducted on formulations with trade names thus directly helping the manufacturers to increase their sales. Once the results of such trials are available, they are misused to induce practitioners of modern medicine to prescribe, an illegal act. Despite claims to the contrary, Ayurvedic products are not always safe. Many contain minerals and metals such as lead, mercury, arsenic, etc., and have side-effects. They can interact with ingredients of modern medicines about which allopaths are blissfully ignorant. The Medical Council of India should discharge its statutory duty and take urgent steps to ensure that the Supreme Court ruling is obeyed in letter and spirit.

MIMS India, Editorial, May 2005

Guidelines for Rational Use of Drugs

- Prescribing a drug only when genuinely indicated
- Choosing drugs which are effective
- Using single-ingredient drugs
- Using drugs indicated for specific conditions
- Choosing drugs which are relatively safe
- Choosing cheaper alternatives

Some of the steps needed to rationalize the use of drugs in the market are:

- Elimination of new drugs, which are expensive and not necessary because other drugs with proven efficacy already exist in the market.
- Elimination of useless, hazardous and harmful drugs which have irrational combinations.
- Use of Essential Drugs List.
- Marketing of drugs by their generic names.

A Pakistan Network newsletter cartoon promoting the view that not all visitors to a clinic or hospital should leave with a drug; doctors should exercise their right to prescribe a no-drug therapy.

2. Causes of Irrationality

Irrationality in prescription of medicines is of two broad types: using irrational drugs available in the market; and irrational use of rational, essential drugs available. (See box below on *Ten Reasons for Irrational Prescribing*.)

Some of the common irrational prescription and treatment practices include (see box later below on *Specialists and Inappropriate Prescription*):

- Prescribing antibiotics for ailments like diarrhoea or viral infection where they are useless, thus causing antibiotic resistance by the body when these drugs are given for serious infections.
- Prescribing combination products where one medicine is sufficient.
- Prescribing unnecessary and expensive vitamins or tonics, regardless of the condition being treated.
- Prescribing expensive new drugs in preference to established, less expensive ones.
- Ordering of unnecessary investigations.

Who is responsible for allowing irrational drugs and irrational prescriptions? The Government first, the drug companies second, and then the medical profession and their professional associations for not being disciplined enough. We deal with some of the interactions, nexus if you will, between these three segments of our society in subsequent chapters.

Ten Reasons for Irrational Prescribing

1. The belief of a pill for every ill.
2. The more the merrier, combinations work better, and the belief in shotgun therapy.
3. I have to cover all possibilities.
4. The latest is the best (latest antimalarials, antibiotics, analgesics, etc.).
5 Costlier is better, especially with poor quality drugs in the market.
6. My professor said so …
7. The MR (medical representative) said so …
8. The patients demand it (or, I will lose my practice …) …
9. In my experience ...
10. The more I write the more I earn …

SomeFrequentlyAbusedDrugsinIndia,ThankstotheirLarge-ScalePrescription

1. Vitamins 2. Digestives 3. Cough expectorants 4. Antibiotics 5. Injections of all kinds 6. Analgesics 7. Blood (as transfusions)

- Observations of a practising physician doing rational practice

A leaflet from the UK's public education campaign on the correct use of antibiotics.

In general, irrational use of medicines occurs due to:

2.1 Lack of Knowledge

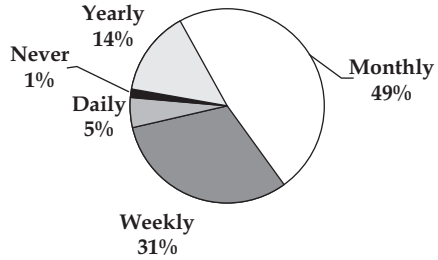
Or when prescribers have no scientific knowledge. This happens as much in the case of so-called quacks or when doctors have not kept abreast of current developments in medicine. It is indeed debatable whether any formally trained doctor with a medical degree who does not have the knowledge to treat even simple problems, or treats common problems irrationally, should be considered a "quack"; likewise, should a well-trained village health worker knowing how to prescribe for specific conditions be considered "practising" medicine unethically and illegally? Again, where do we place doctors who have paid money to buy degrees and trained in medical colleges, with a lack of the required facilities as per the Medical Council "rules" but have managed to get recognition? Lack of knowledge also occurs when patients treat themselves without sufficient knowledge about the drug. Most OTC drugs have instructions for use in English - a language understood only by a minority of the Indian population. Moreover, very often instructions are couched in technical jargon (and often in small, unreadable print), which cannot be understood by laypersons. In addition, people tend to recommend drugs based on their personal experience.

2.2 Inaccurate Diagnosis

This occurs due to lack of interest, lack of time, over-crowded OPDs, inadequate health personnel and lack of diagnostic aids. Diagnostic services are woefully lacking in the public health system in general and in rural areas in particular, where the doctors often function with a complete lack of diagnostic services. It is only now after nearly 60 years of independence, that microscopes are reaching the primary health centres which can diagnose tuberculosis based on sputum examination. When a patient presents with fever of a week's duration, and the doctor is uncertain about whether it is malaria or typhoid, he writes a shotgun prescription which has drugs for both malaria and typhoid.

2.3 Lack of Objective Drug Information

It is doubtful whether the majority of doctors in India are in the habit of referring to standard textbooks or standard medical journals. In Britain, all practising doctors are supplied every six months with a copy of the *British National Formulary* (BNF) which contains reliable, updated information including costs on the preparations on sale in the UK. There is no such widely circulated publication in India, and the British example is highly worthy of emulation. Journals like *BODHI* which aim at providing unbiased information on new drugs need to reach out to a much wider audience. India has a now a number of prescriber handbooks in wide circulation like *MIMS, CIMS, Drugs Today, Indian Drug Review,* which are bought by doctors. The prescribing information in most publications except *MIMS* cannot be relied upon. Some of these journals bring out "Review of New Drugs," which are actually based on unreliable information. These publications even bring out pseudo-scientific reviews of irrational drugs! A widely circulated publication also has in each therapeutic section, after a



Percentage of Doctors That Use Information Provided by Drug Company Representatives in Their Clinical Practice

Quoted in: Heath I (2006) Combating Disease Mongering: Daunting but Nonetheless Essential. *PLoS Med* 3(4): e146

list of allopathic drugs, a list of licensed herbal preparations, without of course any side-effect mentioned!

Doctors in India often do not update their knowledge by referring to standard textbooks and journals. They take the easy way out by relying on information supplied by medical representatives and drug companies which can be very biased and selective (see Chapters 4 and 5). Also, doctors are led to believe a lot of new products are being marketed every day. Many of these are not new discoveries, which radically alter the course of treatment. Therefore to say that it is difficult to keep up with new knowledge does not appear justified. Thirdly, the lack of compulsory recertification of medical degrees and continuing education programmes are other reasons why doctors do not update their knowledge regularly.

Evidence-basedmedicine (see box below *On Evidence-Based Medicine*), the practice of medicine based on scientific evidence combined with sound clinical experience and judgment, is a far cry for many doctors, thanks to the prohibitive cost of journals. But the situation can be redeemed, to some extent, by judicious use of reliable sites in the Internet like that of the Cochrane Collaboration.[1] Or locally affordable journals like *BODHI*.[2] Evidence-based medicine is the larger aspect of rational treatment and rational prescription of medicines.

2.4 Aggressive Drug Promotion: Influencing Doctors

As mentioned in the earlier chapter, there are more than 20,000 formulations in the Indian market, many of which are similar except for different brand names or for a few unnecessary additional ingredients. Pharmaceutical companies therefore indulge in aggressive marketing to promote the sale of their brands. Sometimes, it results in unethical marketing practices such as bribing doctors with diaries, calendars, posters, gifts and even foreign trips and vacations.[11]

The top 50 drug companies in India companies spend Rs. 5,340 crore every year that generates sales of Rs. 28,769 crores; 18.56% of the total income is spent on selling expenses, that is, Rs. 133,500 per doctor per year, which is the highest among all manufacturing activities (Source: *ET Intelligence Group*, Dec 15, 2004).

In a new and more blasé mode of promoting sales of drugs, companies are making overtures directly to doctors for prescribing their drugs in return for a certain consideration. This practice is now spilling over to the prescription and sales of medical devices like intra-ocular lenses, orthopaedic implants, and drug eluting

On Evidence-Based Medicine

"Evidence-based medicine (EBM) is the integration of best research evidence with clinical expertise and patient values …. by patient values we mean the unique preferences, concerns and expectations each patient brings to a clinical encounter and which must be integrated into clinical decisions if they are to serve the patient."[3] A more detailed definition follows.

Traditionally, the practice of medicine has been based on recourse to authority. Even today prescription and health care practices follow fashions or what a revered senior prescriber is seen as doing. EBM is a tool to challenge authority that flows from perceived positions of power in society. Ideally such authority, if at all, needs to be based on scientific expertise, acknowledged by peers. EBM can also help end the "therapeutic nihilism" in mindless prescriptions, in the absence of randomized trial evidence. Evidence-based medicine (EBM) is an antidote to irrational practices in medicine and health care. Properly used, EBM would foster a culture of thinking and taking decisions rationally.

WhatisEvidence-basedMedicine?

"Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. By individual clinical expertise we mean the proficiency and judgment that individual clinicians acquire through clinical experience and clinical practice. Increased expertise is reflected in many ways, but especially in more effective and efficient diagnosis and in the more thoughtful identification and compassionate use of individual patients' predicaments, rights, and preferences in making clinical decisions about their care. By best available external clinical evidence we mean clinically relevant research, often from the basic sciences of medicine, but especially from patient centered clinical research into the accuracy and precision of diagnostic tests (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative, and preventive regimens. External clinical evidence both invalidates previously accepted diagnostic tests and treatments and replaces them with new ones that are more powerful, more accurate, more efficacious, and safer …

… Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough. Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient. Without current best evidence, practice risks becoming rapidly out of date, to the detriment of patients."[4]

DoesProvidingEvidence-BasedCareImproveOutcomesforPatients?[5]

"No such evidence is available from randomized trials because no investigative team or research granting agency has yet overcome the problems of sample-size, contamination, blinding, and long-term follow-up which such a trial requires. Moreover, there are ethical concerns with such a trial: is withholding access to evidence from the control clinicians ethical? On the other hand, population-based "outcomes research" has repeatedly documented that those patients who do receive evidence-based therapies have better outcomes than those who don't.

For positive examples, myocardial infarction survivors prescribed aspirin or beta-blockers have lower mortality rates than those who aren't prescribed these drugs,[6] and where clinicians use more warfarin and stroke unit referrals, stroke mortality declines by >20%.[7] For a negative example, patients undergoing carotid surgery despite failing to meet evidence-based operative criteria, when compared with operated patients who meet those criteria, are more than 3 times as likely to suffer major stroke or death in the next month."[8]

Evidence-based medicine needs firstly formulating the correct question, and then special skills in seeking, sifting and critically evaluating the evidence from published research papers, including the ability to critically appraise patients' stories, symptoms, and signs. "Sometimes research findings may contradict each other and obscure the true picture this is particularly the case with small trials. However, by pooling together all the results of various research studies, the sample size can, in effect, be increased. This is known as meta-analysis. Although pooling together the results of a number of trials will provide a greater weight of evidence, it is still important to examine meta-analyses critically."[9] A badly done meta-analysis can of course mislead.

IsEvidence-BasedMedicinePossibleinIndia?

Often it is felt that in the absence of access to standard journals or reliable database, evidence-based health care is not possible in India. This is a plaint not very justifiable for most urban-based well-to-do practitioners today, especially with access to the Web. Access or not, nothing forbids a prescriber from adopting an attitude of critical questioning in routine medical care. Or question the information put out by drug companies while marketing certain medicines. Or from building a network of conscientious, rational doctors seeking and propagating evidence-based information from the few affordable journals or from creating a system of information sharing.[10] Of course the Drug Controller General of India (DCGI), the Medical Council of India, the ICMR and the many medical professional associations could initiate systems for EBM in India.

coronary stents. A flip chart of a reputed pharma company says it all: "Doctors, you are Partners In Our Progress … and Partners in our Profits."

Some further examples:

- In the past eight years, a South Delhi-based surgeon was sent on vacation to Switzerland by a well-known Delhi based pharma company every year. Quid pro quo: he prescribed only the obliging Company's products. In the case of antibiotics he went one step further. Instead of 5-7 days, the patients were made to swallow the bitter pill for 10 days.
- Johnson & Johnson which produces epoetin alfa (life-saving for kidney transplant patients) was gracious enough to sponsor 300 kidney specialists to visit Singapore for three days. Result: its brand had the highest sale. (Source: "Drug Price Control: Principles, Problems and Prospects," C.M. Gulhati, Editor, *MIMS India*, in *mfc bulletin,* Issue No 305, June-July 2004)

2.5 Over/Under Prescribing by Doctors

Over-prescribing occurs when doctors prescribe drugs in large quantities, for too long duration, too many at the same time for the same problem, or sometimes even unnecessary drugs. This is a wastage of money and drugs, causes adverse reactions due to drug interactions, and worst of all does not improve the patient's condition, which may deteriorate. Doctors over-prescribe because they may not be able to diagnose the patient's condition and hope to "hit or miss" with a wide range of drugs. They may also be influenced by the pharmaceutical companies, which supply doctors with excessive samples. In addition, doctors may not be able to resist patients' demands for more medicines, lest they lose their practice to a competing private practitioner. On the other hand, under-prescribing occurs, among other reasons, due to lack of knowledge on the part of the prescriber, non-availability of drugs as in the case of long-term, regular treatment necessary for the treatment of diseases like tuberculosis and leprosy, and patients' inability to purchase drugs. Many disorders are under treated in medical practice, and many effective drugs are underused. A classic example is that of ORS in children with diarrhea. Another important example is that of hypertension. Hypertension is a disease, which in the large majority of patients is without any symptoms. It is a silent killer since it can lead to stroke, heart attacks, and kidney failure. All adults should be screened for the presence of hypertension, yet this is hardly done in health facilities in India and as a result most patients with hypertension are not detected and treated appropriately in India. Indeed it is usual for patients to be detected as having hypertension only when they develop a stroke, or a cardiac complication.

Source: Prescrire

2.6 Cut-Practice

Another reason for irrational and often expensive treatment is the phenomenon of cut practice, that is, kickbacks and commissions offered by specialists, pathologists, X-ray clinics, CAT scan centers, etc., to prescribers who refer patients to them. As a result unnecessary tests, and procedures are ordered on unsuspecting patients.

Specialists and Inappropriate Prescription

Prescription patterns reflect the frequency of visits by medical representatives, particularly high among medical teachers and busy consultants. Studies suggest that attendance at 'scientific' company-sponsored symposia and acceptance of pharmaceutical companies' publications 'alter physicians' prescribing practices and patient care", often resulting in their prescribing inappropriate and expensive drugs even for unapproved indications. All doctors working for the Bangladesh government, including professors of medical institutes, are free to indulge in unlimited private practice. Doctors in a position of authority and influence are encouraged by drug companies to attend company-sponsored seminars in their own countries and abroad.

This practice is rife in industrialized countries. One survey in Canada revealed that 17 percent of doctors had their travel expenses and conference fees paid by pharmaceutical companies and 3 percent were presented with computer equipment. Unfortunately, many symposium proceedings are later published in well-known journals with financing from the same sponsor; the British Medical Journal, the Lancet, the New England Journal of Medicine and the Journal of the American Medical Association are notable exceptions to the plethora of medical journals, which publish drug companies' symposium proceedings (see table below).

These journals are then distributed free to other, less senior doctors to make sure that they too prescribe the new, often dubious products. Such publications also promote untested new technology. The prescriptions issued by senior physicians are immediately copied by juniors, and gradually by general practitioners and by unqualified doctors. This tendency is pronounced in Third World countries.

Number of Symposia Proceedings Published in Selected Journals

Journals	*Number of symposia proceedings published*	
	1966-1979	*1980-1989*
American Journal of Cardiology	32	79
American Heart Journal	0	25
Hypertension	0	17
Circulation	3	11
American Journal of Medicine	18	67
American Journal of Obstetrics	0	10
British Journal of Anaesthesia	5	11
Cancer	6	13
Journal of Allergy Immunology (Clinical)	1	11
Kidney International	5	23
Transplantation Proceedings	6	56
British Medical Journal	0	0
New England Journal of Medicine	0	0
Lancet	0	0
JAMA	0	0

Source: Bero, L.A. et al. "The Publication of Sponsored Symposiums in Medical Journals". *New England Journal of Medicine*, October 15, 1992.

Drugs of doubtful value such as vinpocetine (brand name Cavinton, from Medimpex of Hungary), bencyclane hydrogen fumerate (brand name Fludilat, from Organon) and oxpentifylline (brand name Trental, from Hoechst)

appear remarkably frequently in the prescriptions written by senior teachers of neuromedicine. These drugs, at best of doubtful efficacy, at worst useless, remain in Bangladesh because of the persistent pressure by well-known senior professors for their retention.

Another concern is misprescription, such as the prescribing by gastroenterologists and other specialists of pancreatin enzyme (brand names Festal, from Hoechst, and Zymet, from Beximco) and oxiphenomonium bromide (brand name Antrenyl, from Ciba-Geigy) for indigestion. Some brands are more misused than others in the same category of drugs, obviously because of heavy promotion. Interestingly, drugs of doubtful efficacy are highly priced. A 250 mg tablet of ciprofloxacin, a useful drug but wrongly prescribed for ordinary fevers of two to three days' duration and for diarrhoea, cost Taka 12 in 1994, whereas cotrimoxazole cost just over Taka 1 per tablet. Similarly, a 300 mg ranitidine tablet was priced at Taka 4, while 20 mg of omeprazole cost Taka 14. Not only do bribes in the form of gifts, or travel and per diem expenses for attendance at seminars, increase the irrational prescription of drugs, they also add to the cost of these unnecessary drugs. An extensive study of prescribing habits of GPs and paediatricians in Indonesia, undertaken in 1988 by the Indonesian Consumer Federation found that GPs wrote fewer drugs per prescription than paediatricians. Paediatricians also often wrote two or more antibiotics in the same prescription (in 21.1 per cent of cases compared with 12.4 per cent for GPs). GPs prescribed two or more vitamins (15.8 per cent) and two or more antidiarrhoeal drugs (31.6 per cent) in the same prescription, a higher incidence than for paediatricians. But oral rehydration therapy (ORT), generally acknowledged to be the most important and effective form of treatment for diarrhoea, had been prescribed in only 16.03 percent of all the cases.

Source: Chowdhury, Zafrullah. *The Politics of Essential Drugs*. Vistaar Publications, New Delhi, 1995, pp.124-126.

2.7 Availability of Irrational Drugs in the Market[12]

One of the root causes for irrational prescriptions are irrational fixed dose combination drugs, costly tonics, and increasingly, food supplements (marketed as "nutraceuticals"). We discuss them later below.

Is our country that short of doctors ?

2.8 Presumed Patient Demand

Doctors justify the practice of a pill or more for every ill by stating that patients expect and demand medicines. This is partly true, but this reason does not in any way give the doctor the license to prescribe unnecessary, unscientific, and costly medicines. In reality, a clearer delineation of the problem (e.g., many patients with multiple symptoms often have underlying illnesses like depression), explanations about the nature of the problem and a sympathetic attitude work better than a host of medicines prescribed.

2.9. Self-Medication by Patients

Patients can be irrational about the use of drugs. Often even rational prescriptions of doctors are not followed and therapy is modified or prematurely discontinued. In a situation where prescription drugs are available over the counter it is common for patients in India to pop pills like antibiotics without seeking a medical opinion. Often the drug bought is one which is mentioned in a past prescription and which worked in a similar problem.

Among lay people there is concern about the side-effects of allopathic medicines and a belief that alternative

medicines like Ayurveda, Siddha, or homoeopathy do not have any side-effects. This belief is incorrect as any substance which is capable of exerting an influence on a disease process, is also capable of producing side-effects in case of incorrect use and incorrect dosage. In fact, Ayurvedic remedies contain substances like aconite as well as heavy metals which have known toxicity on the human body. Authentic Ayurvedic texts recommend elaborate precautions for detoxifying these substances, which are unlikely to be carried out in the current scenario of mass manufacture of Ayurvedic drugs. There are numerous reports of heavy metal poisoning related to some Ayurvedic drugs in the scientific literature. These include a report of the highest reported lead concentration in a newborn child wh

2.10 Dispensing by Chemists in India

At any chemist's store in the smaller cities and towns of India , it is a common to see people approaching the chemist himself for relief of some symptoms like pain, or fever and cough, or diarrhoea. They then buy prescription drugs over the counter, prescribed by the chemist. Most often these drugs do not conform to any rational process of selection and use. This practice is so prevalent, that some companies now promote drugs to chemists directly. These drugs often have very high maximum retail price compared to their rates to the retailer. For example, cetrizine has a rate to the retailer of 21 paise, yet has MRP of Rs. 2.60 paise per tablet. Two other products, like omeprazole (for peptic ulcer and gastroesophageal reflux), and nimesulide (a pain-killer which is known to have hazardous side-effects), were also found in an investigation by the Ministry of Chemicals itself to have trade margins of over 1000%: a windfall indeed for chemists doubling up as a prescriber.

2.11 Informal/Untrained Practitioners in India, Especially in Rural Areas

Access to health care of even uncertain quality is a huge problem for the vast population which lives in rural India. The public health system in the rural areas is acknowledged in the National Health Policy document of 2002 to be dysfunctional and lacking in essential drugs and services. For many people living in difficult terrains in hills, close to forests, etc., this problem is particularly acute. The vast need for some form of curative care is partly met by a million-strong cadre of informal, untrained practitioners (or the "jhola-chapp" doctors) or so-called quacks, often drawn from the very communities whom they cater to. In a state of complete absence of healthcare services, they are sometimes a necessary evil. Necessary because they often provide some access to drugs; and evil because their practices cause major complications for the patients. Patients of virtually any age or illness are treated with an injection which often is a cocktail of drugs containing an antibiotic, steroid, and an antihistaminic. The injections that they administer are almost always unsafe with a brief dip into lukewarm water and some disinfectant like Dettol, serving as an apology for sterilization. The quacks with their unsafe injection practices are contributing to the spread of blood-borne pathogens like Hepatitis B, Hepatitis C and HIV/AIDS. Patients with TB often have their diagnosis delayed for months because of such practitioners providing those cough syrups, tonics, saline infusions, thus delaying a correct diagnosis. Women in labour facing some delay are injected repeatedly with oxytocin injections often making the problem worse for both the mother and the unborn child. Women are subjected to medical terminations of pregnancy with unsafe procedures and unsterile conditions and a large number develop septic abortions as a result. These quacks are often closely linked to private practitioners operating in towns and smaller cities and act as the source of patients for their practice.

[i] "Severe congenital lead poisoning in a preterm infant due to a herbal remedy." Tait PA, et al. *Medical Journal of Australia.* 2002; 177(4): 193-5.

2.12 Disease Mongering by Drug Companies

We discuss this issue in Chapter 5 along with Drug Promotion, Clinical Trials, and Conflicts of Interest between Medical Profession and Drug Industry.

2.13 Implications of Irrational Use of Drugs

The problem of irrational use of drugs has reached such proportions and has such implications that it cannot be regarded as a mere nuisance. It is a major public health problem by itself. Some of the implications are:

- **Colossal Wastage of People's Resources:** The Report of the National Commission of Macroeconomics and Health mentions that out of the top-selling 25 brands in India, 10 were irrational. Even if a consider a conservative figure of 10% of the overall preparations as being irrational, the turnover related to the sales would be more than Rs 2000 crore. This figure is more than the combined budgets of the Central and State Governments on procurement of drugs. The hard-earned money, or money borrowed at usurious rates of interest, is being used in the purchase of therapeutically ineffective and unnecessary medicines.

- **Risk of Adverse Effects:** All drugs carry the risk of side-effects, e.g., majority of the pain killers carry the risk of side-effects on the stomach. The unnecessary use of drugs exposes patients to the risk of side-effects. About 4 % to 10% of hospital in-patients suffer an adverse drug reaction in developed countries. This is the fourth to sixth leading cause of death in the US and costs $130 billion in the US and 466 million pound sterling in the UK yearly.[i]

- **Risk of Antimicrobial Resistance:** Globally there is a rise in the resistance to antibiotics and a major cause is the wrong use of these medicines.

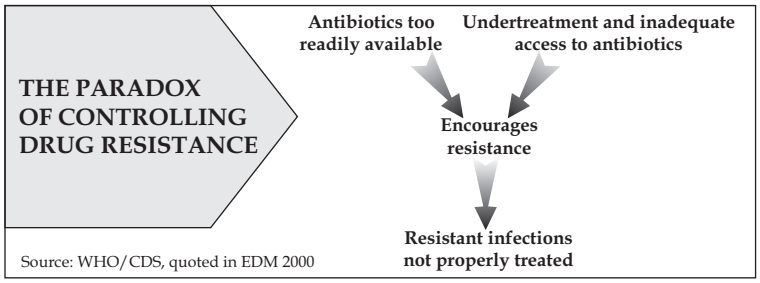
- **Risk of Transmission of Diseases through Unsafe Injections:** Unsafe and unnecessary injections are one of the biggest and most dangerous manifestations of irrational use of drugs in India. A nationwide study conducted in 2003-04 by the India CLEN Programme Evaluation Network (see <http://www.inclentrust.org/>), provided startling rates of unsafe injections in India. An average Indian receives 2.9-5.8 injections per year, making it 3-6 billion injections per year. Almost every other prescription (48.1 percent) resulted in an injection. The safety of such injections was abysmal with 62.9 per cent of injections being adjudged as unsafe and nearly 32 per cent were considered to be capable of transmitting serious blood-borne viral infections.

  A proof of the hazard of unsafe injections has been in outbreaks of hepatitis B with high fatality documented and reported by the National Institute of Communicable Diseases in the recent years from villages in rural Haryana and rural Gujarat. In Dhottar village of Sirsa, Hepatitis B related to unnecessary injections by practitioner caused 54 cases of jaundice over a 8-month period of which

[i] "Irrational drug use causing rise of anti-microbial resistance", *TWN Info Service on Health Issues* No. 9 by Martin Khor, Geneva, 26 May 2005.

18 people died.[i] Worldwide these disturbing figures have been corroborated. According to estimates published in the *Bulletin of the WHO* in 1999, unsafe injections contribute to 80,000-160,000 HIV infections, 2.7-4.7 million Hepatitis C virus infections, and 8-1.6 million Hepatitis B virus infections globally every year.[ii] An April 2005 WHO policy paper on "Containing anti-microbial resistance" says that anti-microbial resistance is one of the world's most serious public health problems. Many of the microbes that cause infectious disease no longer respond to common anti-microbial drugs such as antibiotics, antiviral and antiprotozoal drugs.[iii] "The problem is so serious that unless concerted action is taken worldwide, we run the risk of returning to the pre-antibiotic era when many more children than now died of infectious diseases and major surgery was impossible due to the risk of infection."

WHO country data of 2002-03 shows the following global anti-microbial resistance prevalence rates: malaria (chloroquine resistance in 81 out of 92 countries); tuberculosis (0-17% primary multi-drug resistance); HIV/AIDS (0-25% primary resistance to at least one antiretroviral drug); gonorrhoea (5-98% penicillin resistance); pneumonia and bacterial meningitis (0-70% penicillin resistance in streptococcus pneumonia); diarrhoea: shigellosis (10-90% ampicillin resistance, 5-95% cotrimoxazole resistance); hospital infections (0-70% resistance of staphylococcus aureus to all penicillins and cephalosporins).


THE PARADOX OF CONTROLLING DRUG RESISTANCE
Antibiotics too readily available
Undertreatment and inadequate access to antibiotics
Encourages resistance
Resistant infections not properly treated
Source: WHO/CDS, quoted in EDM 2000

Antibiotic Discovery and Resistance Development

Antibiotic	Discovered	Introduced into clinical use	Resistance identified
Penicillin	1940	1943	1940 (methicillin 1965)
Streptomycin	1944	1947	1947, 1956
Tetracycline	1948	1952	1956
Erythromycin	1952	1955	1956
Vancomycin	1956	1972	1987
Gentamicin	1963	1967	1970

Source: CIBA Foundation, quoted in *Antibiotic resistance: synthesis of recommendations by expert policy groups.* WHO, Geneva, 2001.

RESISTANCE CAN BE EFFECTIVELY TREATED

Ideal drug usage involves:
- The correct drug
- Administered by the best route
- In the right amount
- At optimum intervals
- For the appropriate period
- After an accurate diagnosis

Problems occur in both developed and developing countries when antimicrobials are:
- Not equitably available
- Used by too many people
- To treat the wrong disease
- In the wrong dosage
- For the wrong period of time
- Not in the correct formulation or strength

Antimicrobial resistance is not a new or surprising phenomenon. All micro-organisms have the ability to evolve various ways of protecting themselves from attack BUT over the last decade or so:
- Antimicrobial resistance has increased
- The pace of development for new and replacement antimicrobials has decreased.

RESISTANCE MEANS THAT:
- People can't be effectively treated
- People are ill for longer
- People are at greater risk of dying
- Epidemics are prolonged
- Others are at greater risk of infection

Source: WHO/CDS

[i] Singh J, Gupta S, Khare S, Bhatia R, Jain DC, Sokhey J. National Institute of Communicable Diseases, Delhi, India *Epidemiol Infect.* 2000 Dec; 125(3):693-9. A severe and explosive outbreak of hepatitis B in a rural population in Sirsa district, Haryana, India: unnecessary therapeutic injections were a major risk factor.

[ii] Kane A, et al. Transmission of Hepatitis B, Hepatitis C and Human Immunodeficiency Virus infections through unsafe injections in the developing world. Model based regional estimates. *Bulletin of WHO* 1999:77 (10).

[iii] See also: Containing Antimicrobial Resistance: Review of the Literature and Report of a WHO Workshop on the Development of a Global Strategy for the Containment of Antimicrobial Resistance. Geneva, Switzerland, 4-5 February 1999 at <http://www.who.int/csr/resources/publications/drugresist/WHO_CDS_CSR_DRS_99_2/en/>. Also see <http://www.cdc.gov/drugresistance/>.

3. Combination Drugs: When Drug Combinations are Rational

Drug combinations in some cases are not only rational but are sometimes even necessary.

The scientific rationale of few selected drug combinations is given below:

1. When it allows synergistic action, i.e., it facilitates each other's pharmacological action, thereby producing greater effects.
2. Where it allows enhanced efficacy without linking of each other's pharmaco-chemical actions.
3. Combined doses are given in cases of general under-nourishment or simultaneous deficiency of all vitamins in famine conditions, e.g., Vitamin B complex, multivitamin, ferrous sulfate + folic acid, Vitamin A + Vitamin D.
4. Where it is necessary to reduce side-effects or toxicity, e.g., isonex + Vitamin B6 (Vitamin B6 prevents peripheral neuritis caused by prolonged use of isonex).

According to the WHO Expert Committee[13] combination drugs should not be used unless there are no alternative single drugs available for treatment or no alternative single drug was cost-effective for the purpose. Experts recommend that patients be individually evaluated and those patients requiring more than one drug should be prescribed separately. Combination drugs "increase the risk of side-effects and may also needlessly increase cost while encouraging irrational 'miss and hit' therapy."[14] When a combination drug is used it is difficult to identify which of the constituent drugs is the cause of a drug reaction. Combination drugs are irrational also because their stability is doubtful, reducing the efficacy in many preparations.[15] Moreover, drug companies frequently change the ingredients making it difficult to keep track of the changes.

Injections with combination of streptomycin (for the treatment of TB) and penicillin, since banned, have been widely used in the treatment of fevers, infections and other minor illnesses. This is irrational because it masks the occurrence of TB and leads to the development of resistance to streptomycin by TB Bacilli (mycobacterium tuberculosis). Similarly, streptomycin in combination with chloramphenicol was widely (mis)used in the treatment of diarrhoea (the combination has been banned since 1988 after attempts by affected drug companies to thwart a ban). This was a sheer waste as 60 per cent of diarrhoeal diseases are viral in origin and can be controlled by Oral Rehydration Therapy and do not need antibacterials. Indiscriminate use of chloramphenicol itself is hazardous because it unnecessarily exposes people to the risks of chloramphenicol, for example fatal blood disorders like agranulocytosis. The drug should be reserved for typhoid fevers. Used in combination, it causes
reserved for typhoid fevers.

Irrational drug combinations include:

- Antibiotics combined with other antibiotics or with corticosteroids or other active substances such as vitamins.
- Combinations of antipyretics and analgesics, e.g., ibuprofen + paracetemol or analgin + paracetemol.
- Analgesics combined with iron, vitamins or alcohol: Combination painkillers increase the risk of toxicity

Irrational combination

and other side-effects, especially kidney damage. Analgesics combined with iron or vitamins are irrational and wasteful; analgesics combined with alcohol are wasteful and potentially dangerous.

- Codeine in combination with other medicines: since codeine is a habit-forming drug and using it in combination medicines increases the risk of addiction.
- "Multi" and liquid vitamin preparations, with the exception of combination vitamins supplied in small bottles, with droppers for babies.

The guidelines as per the WHO recommendations for acceptability of Fixed Dose Combinations are:

1. Clinical documentation justifies the concomitant use of more than one drug.
2. Therapeutic effect is greater than the sum of the effect of each.
3. The cost of combination product is less than the sum of individual products.
4. Compliance is improved (that is when two or more medicines are to be taken separately, as in the case of TB, the user tends to avoid one or two medicines after sometime. This can be avoided if all three medicines are combined into one).
5. Sufficient drug ratios are provided to allow dosage adjustments satisfactory for the majority of the population.

Any fixed dose combination, which does not satisfy the above-mentioned guidelines, is considered irrational. (See also Annexure 1: *Why some leading drug combinations in the Indian market should not be sold - but are still sold.* Also the box below *Combinations and "Irresponsible Conduct of State Drug Controllers".* Also see Annexure 2 for a partial list of irrational combinations.)

Combinations and "Irresponsible Conduct of State Drug Controllers"

… most of the fixed dose combinations currently marketed in India are not at all rational as their clinical benefits are in doubt but the licenses were issued for their manufacture and marketing. The state drug controllers in India have been either not looking into the aspect of drug safety or have been issuing licenses under the influence of other considerations. The office of the DCGI had often cautioned the state drug controllers against this practice in the past but with no result. Such excesses on the part of the state drug controllers have been, in fact, a contravention of the provisions of the Drugs and Cosmetics Act. The Act clearly states that permission for the manufacture and marketing of any new drug has to be obtained from the DCGI

Perhaps the sole reason for the presence of thousands of irrational and harmful combinations in the Indian pharmaceuticals market is this irresponsible conduct of state drug controllers. Fixed dose combinations of ciprofloxacin with tinidazole, amlodipine with lozarten and nifedipine with atenolol are in hundreds in the market with no therapeutic rationale. In the case of nimesulide, there are as many as 130 combinations. Many more such drug combinations are getting approved in various parts of the country and getting into the market. It is significant to note, in this context, that DCGI, last week asked the state drug controllers to withdraw all manufacturing licenses issued by them for drug combinations after May 2002. The DCGI action comes in the wake of a recommendation in this regard by the Drug Consultative Committee to the Central government. It is certainly a bold move and the office of DCGI should put maximum pressure to get it enforced in the states this time. It is to be recalled that DCGI had prohibited the state drug controllers from issuing any more licenses for new combinations in a directive in November 2001. But this directive was more ignored than followed by the state drug controllers.

Source: "Action on Combinations", Editorial by P A Francis, July 07, 2004 at <www.pharmabiz.com>

There are also some simple ways of monitoring drug use. See for example the box below on Core Drug Use Indicators. (See also Phadke,[16] for a critique of these criteria.)

Core Drug Use Indicators

Prescribingindicators

1. Average number of drugs per encounter
2. Percentage of drugs prescribed by generic name
3. Percentage of encounters with an antibiotic prescribed
4. Percentage of encounters with an injection prescribed
5. Percentage of drugs prescribed from essential drugs list or formulary

Patientcareindicators

6. Average consultation time
7. Average dispensing time
8. Percentage of drugs actually dispensed
9. Percentage of drugs adequately labelled
10. Patient's knowledge of correct dosage

Facilityindicators

11. Availability of copy of essential drugs list or formulary
12. Availability of key drugs

Source: *How to Investigate Drug Use in Health Facilities: Selected Drug Use of Indicators. Action Programme on Essential Drugs*, WHO, Geneva, 1993.

4. Vitamins and Tonics

These are some of the most highly selling and highly priced products in India. Vitamin and tonics are in many cases a mixture of Vitamin B-complex or vitamins in solutions of sugar and alcohol. Tonics or health restoratives are prescribed for debilitating conditions, usually for convalescents, chronic diseases, loss of appetite, weight loss, and fatigue.

Among the top-selling 25 medicines in India are Becosules, Neurobion and Dexorange; the first two are irrational and/or unnecessary multivitamin preparations and the last is an irrational iron "tonic" (see Chapter 4 and Section 5.5 of this chapter for more on Dexorange).

Vitamin and tonic preparations are irrational because what is actually needed is an adequate mixed diet containing leafy vegetables. Vitamin deficiency should be treated with specific vitamins in dry tablet form.

Tonics are hazardous when substances like caffeine, leptazol are combined with vitamins. Regular intake of Vitamin A and D can be excessive and hence hazardous.

Bangladesh had banned tonics, enzyme mixtures/preparations and restorative product because such products "flourish on consumer ignorance... most are habit-forming and with the exception of pancreatin and lactase (which are allowed as single ingredient products) of no therapeutic value."[17] The United Kingdom does not recognize tonics as drugs.

Most of the tonics are grossly advertised with many tall claims as health restoratives. However they often contain inadequate doses of vitamins, useless ingredients and a lot of alcohol. A well-known tonic, Waterbury's Yellow Label tonic, contained about 3 mg of iron per teaspoon of which only one-tenth is absorbed by the body. The Indian Council of Medical Research recommends at least a daily intake of 10 mg for men and 20-30 mg for an average woman.

Some tonic preparations contain more vitamins than what is actually needed. High-potency multivitamin formulations are a sheer waste of resources as they are almost wholly rejected by the body, particularly in the case of well-fed consumers. The daily requirement of the human body of Vitamin C is about 50 milligram, of Vitamin B_1 one milligram and some others in minute quantities of few milligrams. Yet tonic preparations, apart from being extremely expensive, contain between 10 to 50 times the minimum requirements which are simply excreted by the body. Moreover, most vitamins are needed in small amounts to stimulate metabolism, they are not energy-enhancers. Also, there seems to be no scientific rationale for introducing calcium or manganese glycerophosphates in tonics.

The daily requirements of Vitamin C can be obtained from regular use of fruits or fresh vegetables and salad helpings. Vitamin A, supplied by green leafy vegetables, is stored in large amounts by the body for proper vision. Vitamin D is naturally synthesized by the skin from daily sunlight. Despite the availability of inexpensive fresh fruits and vegetables, tonics are a craze among people. Over 15, 000 tonnes of health drinks are produced every year in India. Manufacturers spend a large amount of money on advertisements. Television advertising is a very effective way of getting credulous consumers hooked on these expensive junk. And the current trend is to recommend tonics for healthy adults and growing children.

The production of the high-potency or "Forte" preparations of multivitamins is a sheer economic waste. It is a drain on the consumers and government dispensaries. It would benefit more patients if the preparation was made available in smaller but adequate quantities so that more tablets could be produced at cheaper price. High-potency preparations are also a drain on the country's foreign exchange as most of the raw materials have to be imported.

In a study from Goa,[18] the authors reported after analyzing 990 prescriptions, that "polypharmacy was the norm, with 80% of prescriptions having more than one medicine, with a significant proportion of patients receiving 5 or more preparations. Since many preparations were multi-drug combinations, the actual number of specific pharmaceutical entities prescribed was likely to be even higher. Vitamins and tonics, for which there are few specific medical indications, were used in almost half of all prescriptions. Antibiotics, analgesics and drugs for dyspepsia were prescribed in almost a quarter of prescriptions."

Cough Syrups and expectorants are mixtures of drugs which stimulate coughing (ammonium chloride, ipecac) as well as those which suppress coughing (codeine, noscapine) and antihistamines that dry the secretions.

Prolonged use of cough syrup is habit-forming, it may cause stomach upsets, reduce food intake and cause drowsiness. Corex, one of the top-selling drugs in India (for a list, see Table 5, Chapter 4), is marketed as a cough suppressant but it is very popular in Northeast India, for its addictive presence of codeine.

Coughing is a protective activity of the body. It should not be suppressed except in certain conditions. Simple steam inhalation is advised. If it is necessary to use drugs, use only a single ingredient cough suppressant such as codeine or dextromethorphan. There is no scientific basis for using cough suppressants and cough stimulants together.

The WHO List of Essential Drugs does not include cough syrups and lozenges. Bangladesh has banned them on the grounds of being "of little or no therapeutic value and amounts to great wastage of meager resources."[19]

Another area of gross irrationality is the category known as nutraceuticals: nutritional supplements and health drinks: they are a big market, often promising magic remedy or magic recovery to the consumer when there is no basis for such a promise.

5. Hazardous Drugs[20]

Drugs are hazardous when their risks far outweigh their benefits. Some are toxic and should be used only in life-threatening conditions. Quite a few of them are used in combination and are potentially hazardous.

5.1 Some Commonly used Drugs known to be Hazardous

Analgin or dipyrone is an analgesic pain killer with anti-inflammatory and anti-pyretic (fever-reducing) properties. Its side-effects are severe allergic reactions or life-threatening blood disorders called "aplastic anaemia". It has caused the death of 94 people in Germany between 1981 and 1986. Because of these deaths, the German drug regulatory authority has placed all dipyrone products under prescription and severely restricted their use to post-surgical conditions. Yet analgin, commonly available as Novalgin (Aventis), is one of the more top-selling over-the-counter drugs among consumers, rather than its safer and cheaper alternative, aspirin. FDCs of analgin with any other drug have been banned in India for over 15 years.

Anabolic Steroids (synthetic male hormones) are often used to treat conditions for which they are not only useless but also very dangerous. They are useful as supportive therapy in treating rare conditions such as aplastic anaemia (bone marrow shut down) where the patient is very ill. Instead, anabolic steroids are sold over the counter as appetite stimulants and tonics in the developing countries. These drugs can stunt growth in children by prematurely closing the epiphyses (the growing ends of the bones). They also disturb the sexual development of adolescent children. Young girls can develop masculine characteristics such as deep voice and growth of facial hair, while young boys can develop breasts. These changes are irreversible.

Chloramphenicol is an effective and cheap drug to treat typhoid. It should not be given to treat patients with less serious bacterial infection. Chloramphenicol when used in diarrhoea only prolongs the disease. A child with diarrhoea who is given chloramphenicol faces the risk of possible fatal side-effects while not gaining any benefits. Streptomycin is not absorbed when given by mouth. Hence the drug is not effective in diarrhoea. The combination of chloramphenicol and streptomycin (banned since 1988) would cause diarrhoea because of infection due to change in the gut flora. Commonly available brands of combined chloramphenicol and streptomycin used to be Chlorostrep, Enterostrep, Streptoparaxin, Lifstrep, Streptchlor, Intestotrep. Most diarrhoeas can be treated effectively by means of oral rehydration therapy. It is simple and inexpensive. If drugs need to be used, cotrimoxazole or amoxicillin is a safer and more effective alternative.

Clioquinol was used widely to treat diarrhoea. Marketed as Entero Vioform and Mexaform, it was available over-the counter for the common ailment, "traveller's diarrhoea". It damages the central nervous system resulting in paralysis, blindness and loss of bladder control. About eleven thousand people in Japan were victims of these side-effects caused by the drug. The Swiss drug company, Ciba-Geigy, was found guilty of marketing this drug without revealing its hazards. It is now available and sold as a prescription drug.

Depo Provera is an injectable contraceptive for use by women manufactured by the American multinational, Upjohn. This drug is not allowed for use as contraceptive in USA, but may be prescribed by a doctor after the woman gives her informed consent. Yet the drug is sold in the Third World for contraceptive use. The drug is associated with breast and endometrial cancers, osteoporosis, lowered life expectancy and lowered resistance to infection. In addition, the drug causes severe birth defects if a woman who is unaware of her pregnancy, takes the drug. The effect of the drug on babies when it passes through breast milk is not well documented, but it could interfere with the babies' normal development and inhibit the transmission of immunity. Despite this knowledge, Upjohn promotes this drug for nursing mothers because the drug does not stop the flow of breast milk. Depo is also known to cause depression, hair loss, headaches, weight gain/loss, menstrual spotting, heavy bleeding, skin changes, nausea and loss of libido. Though the drug dosage was originally designed for the larger western women, it has not been decreased proportionately for the smaller Asian women who are now the target for this drug.[21]

Oxyphenbutazone and Phenylbutazone have caused over a 1000 deaths worldwide. It is recommended by the Drug Controller of India only for ankylosyting spondylitis and acute gouty arthritis, and that too only as drugs of second choice. Because of its severe side-effects, Ciba-Geigy has withdrawn this drug marketed as Tanderil. Yet the drug is prescribed widely. (The Supreme Court of India however has banned only fixed dose combinations of Phenylbutazone and Oxyphenbutazone but the individual drugs themselves are still available with potential for continued misuse.)

5.2 Some Banned and Bannable Drugs

Of late in India, the following banned/bannable drugs have also been in the news.

Cisapride: Acidity, constipation. Reason for ban: irregular heartbeat
Brand name: Ciza, Syspride

Droperidol: Anti-depressant. Reason for ban: Irregular heartbeat.
Brand name: Droperol

Furazolidone: Antidiarrhoeal. Reason for ban: Cancer.
Brand name: Furoxone, Lomofen

Nitrofurazone: Antibacterial cream. Reason for ban: Cancer.
Brand name: Furacin

Phenolphthalein: Used in/as Laxative. Reason for ban: Cancer.
Brand name: Agarol

"The evidence we have, Mr Witherington, is that the treatment was a success - it was you that failed ..."

Reproduced by kind permission of J. Collier. Quoted in WHO EDM, Issue No. 31, 2002

Phenylpropanolamine: used in cold and cough medicines. Reason for ban: stroke.
Brand name: D'cold, Vicks Action-500

Piperazine: Anti-worms. Reason for ban: Nerve damage.
Quiniodochlor: Anti-diarrhoeal. Reason for ban: Damage to sight.

5.3 Cox-2 Inhibitors: Rofecoxib, Valdecoxib, Celecoxib, etc.

Internationally, a whole group of "block buster" drugs have been in serious trouble.[22] These include rofecoxib ("Vioxx"), celecoxib ("Celebrex"), valdecoxib ("Bextra"), atoravastin ("Lipitor"), etc. As of writing there is enough evidence to doubt the safety of a host of cyclooxygenase (COX)-2 inhibitors.[23]

The case of rofecoxib is a very instructive one in terms of how a leading MNC drug company with a block buster does anything to ensure its continued presence in the market, how research studies are reported and interpreted selectively and how meta-analyses can be used to support contrary positions, and how the US FDA acts ever so haltingly and indecisively (and India's drug authorities are "conservative" in comparison). It is also instructive in terms of legislative oversight that can put pressure for the better.

Rofecoxib was first marketed by Merck in 1999. The following year, a randomized trial[24] in arthritis patients (VIGOR, the Vioxx GI Outcomes Research study) revealed increased rates of adverse cardiovascular events among patients who took rofecoxib compared with patients who took naproxen. Merck researchers attributed this difference to cardioprotective effects of naproxen, aggressively defended rofecoxib's safety with a series of meta-analyses and retrospective studies, and spent hundreds of millions of dollars marketing rofecoxib to physicians and consumers. More than 80 million people took the drug, which might have caused large numbers of excess serious cardiovascular events.

Merck's eventual decision to withdraw - effective September 30, 2004 - Vioxx from the market was based on new data from a trial called the APPROVe (Adenomatous Polyp Prevention[25] on VIOXX) trial. In the APPROVe trial, Vioxx was compared to placebo (sugar-pill). The purpose of the trial was to see if Vioxx 25 mg was effective in preventing the recurrence of colon polyps. This trial was stopped early because there was an increased risk for serious cardiovascular events, such as heart attacks and strokes, first observed after 18 months of continuous treatment with Vioxx compared with placebo. In addition to its own studies, Merck apparently received information about new research by the FDA that supported previous findings of increased risk of heart attack among rofecoxib users. US FDA analysts estimated that Vioxx caused between 88,000 and 139,000 heart attacks, 30 to 40 percent of which were probably fatal, in the five years the drug was on the market.

The Lancet published a meta-analysis of the available studies on the safety of rofecoxib (Jüni *et al.*, 2004). The authors concluded that, owing to the known cardiovascular risk, rofecoxib should have been withdrawn several years earlier. *The Lancet* published an editorial, which condemned both Merck and the US FDA for the continued availability of rofecoxib from 2000 until the recall. Merck responded by issuing a rebuttal of the Jüni *et al.* meta-analysis (Merck & Co., 2004). In 2005, advisory panels in both the US and Canada encouraged the return of Vioxx to the market, stating that Vioxx's benefits outweighed the risks to patients. The advisory panel's 17-15 ruling allowed the drug to return to the market despite being found to increase heart risk even as public interest groups found evidence of "stacking" and conflicts of interest among the Committee members.[26]

Cardiovascular data from placebo-controlled studies of all three available COX-2 inhibitors were published in 2005.[27] After reviewing these and other findings, an FDA advisory committee recommended that all three COX-2 inhibitors be allowed to remain on the market with expanded safety warnings and without advertising directed at consumers. The vote on celecoxib was a decisive 31:1, but the votes on rofecoxib and valdecoxib were close. Rofecoxib *has not been returned* to the market however. Noting these developments, *the Government of India prohibited sales of rofecoxib and its formulations from December 13, 2004*.

Valdecoxib was eventually withdrawn on April 7, 2005, after a US FDA request asking Pfizer to voluntarily remove Bextra (valdecoxib) from the market, a decision based on an increased incidence of severe skin reactions compared with other nonsteroidal anti-inflammatory drugs (NSAIDs) and evidence of increased risk of cardiovascular malfunction. This decision appeared to validate the analysis of Dr. David Graham, a medical expert at FDA. Graham became a whistleblower[28] rather than keep silent about FDA approved drugs that he perceived as killing people--among these, Vioxx. Dr. Graham's recommendations, which were based on the evidence, were rejected by his bosses at the FDA and by FDA's expert advisory committee, which voted to allow the continued marketing of painkiller drugs that were shown to induce fatal heart attacks and strokes, in February 2005. *The New York Times* reported that 10 of those 32 panelists on FDA's advisory committee who swung the votes had ties with Pfizer and Merck, manufacturers of the drugs in question. It was later revealed by the Center for Science in the Public Interest, that, in fact, 27 of the 32 panelists had financial ties to drug manufacturers.[29]

The Government of India notified a ban on the manufacturing and marketing of valdecoxib formulations in the country effective from July 25, 2005, but not before frenetic lobbying by pharma companies in India to rescind the ban on rofecoxib and desist from any prohibition on valdecoxib. Valdecoxib was subsequently withdrawn both from European markets too. According to the two regulatory agencies, the US Food and Drugs Administration (USFDA) and the European Medical Evaluation Agency (EMEA), valdecoxib poses (a) unacceptable cardiovascular risks, (b) serious, unpredictable, life-threatening skin reactions, and (c) valdecoxib has no advantage compared to other NSAIDs.

Celecoxib (brand Celebrex) is the only COX-2 inhibitor still available; as with all prescription NSAIDs, it now carries a boxed warning regarding cardiovascular and gastrointestinal risks. However the US FDA issued an alert in March 2005 saying: "Based on emerging information, including preliminary reports from one of several long term National Institutes of Health (NIH) prevention studies, the risk of cardiovascular events (composite endpoint including MI, CVA and death) may be increased in patients receiving Celebrex. FDA will be analyzing all available information from these studies to determine whether additional regulatory action is needed."

The Drug Controller General of India (DCGI) has asked drug companies to carry a warning on the label of selected Cox-2 inhibitors: "This drug should be used with caution in patients from Coronary Heart Disease (CHD)/Cardiovascular Disease".

In August 2005, a Texas jury awarded a US$253 million settlement to the widow of a man who died of an arrhythmia (rapid heart beats) while taking rofecoxib. Three months later in New Jersey, Merck was found not liable for an MI that occurred while the plaintiff was taking rofecoxib. Thousands of rofecoxib-related lawsuits are still pending.[30]

Finally, in December 2005, the *New England Journal of Medicine* raised a new "concern" (*N Engl J Med* 2005 Dec 29; 353:2813) that study authors might have deliberately withheld data about myocardial infarctions when they reported results from the critical 2000 VIGOR trial, which established rofecoxib's gastro-protective qualities but also suggested that it might cause excess cardiovascular morbidity.[31]

5.4 Nimesulide: in the Wonderland that is India

Nimesulide was discovered by an American company, 3M Pharmaceuticals, but never got approval for use in the US, Canada, Britain, Australia, New Zealand and 140 other countries around the world.

The case of how nimesulide has been allowed to continue in India is indicative of how decisions regarding problem drugs are taken in India. In India, marketing approval for the drug was granted in 1994 for painful inflammatory febrile disorders but it is being promoted as first line antipyretic therapy.

Numerous studies have established the life-threatening adverse events with nimesulide such as hepatotoxicity, renal toxicity, severe skin reactions including fixed eruptions, gastrointestinal toxicity, potentiation of seizures, potentiation of colitis in passive cigarette smoking. Studies have also shown that nimesulide should not be used as the primary mode of treatment as an antipyretic or analgesic, especially in children, for whom much better and safer choices are available. There is no reason for selecting nimesulide as the first drug of choice for fever or pain.

Subequently, nimesulide was banned in Spain and Finland in 2001 on reports of its hepatotoxicity. Even in Sri Lanka and Bangladesh, nimesulide is not allowed to be marketed. Around August 2003, the European Medicine Evaluation Agency (EMEA) had banned the use of nimesulide in all the 25-member countries. Even in adults, its use has been restricted to acute pain, osteoarthritis, and dysmenorrhoea. Its use for fever is not permitted. Also, it cannot be used for dental diseases such as pain and inflammation. Its topical form is to be used only for relief of pain due to sprains and acute inflammation of tendons due to injury (traumatic tendonitis) only.

Abundance of Nimesulide Formulations

"... 200 nimesulide formulations marketed in the country are without the approval of Drugs Controller General of India. Out of these 200 products, 70 are nimesulide suspensions and the remaining 130 are fixed dose combinations of nimesulide with a number of other drugs. Combinations of nimesulide and paracetamol, numbering 50, are the largest segment in this group. Combinations of nimesulide and two muscle relaxants namely tizanidine and serratiopeptidase with as many as 52 brands are the other two major combination groups. Top selling brands in all the three categories are being marketed by major pharmaceutical companies in the country. What is astonishing here is that so many irrational combinations of nimesulide are being marketed in the country at a time the very safety of this drug is under a cloud ..." [32]

... Nise (nimesulide) is the top-selling analgesic in India and there are a number of me-too irrational combination formulations of nimesulide when the drug itself has been discarded in several countries on safety concerns.[33]

Source: P A Francis: "Vicious Circle of Combinations", *Pharmabiz.com*

The Drugs Controller General of India (DCGI), earlier in his response to a Public Interest Litigation (PIL), filed by Social Jurist, an NGO, seeking a ban on nimesulide, informed the Delhi High Court that there was no reason to ban the drug in India. There are over 70 brands of nimesulide paediatric suspensions in the Indian market, including Nise of Dr. Reddy's Labs and Nimulid of Panacea Biotec. The two account for more than 50 per cent of the market. And the nimesulide market then was of the order of Rs 700 crores with markups over 1500 percent. Since then prices have come down, though not the share of imesulide sales of various companies.

The European decision instead of turning many medical faces red in India, left them unfazed by and large. In a peculiarly Indian twist to evidence-based medicine, on the basis of an "opinion poll" among just 50 doctors of the over 400,000 doctors, the Indian Medical Association (IMA), Delhi branch, came to the conclusion that nimesulide was "safe and effective for all age groups starting with day one to over 60 years" for a variety of conditions, including fever. In the wake of media reports on the drug during 2003, the Indian Academy of Paediatrics (IAP) also advocated continued use of nimesulide by Indian children. Earlier the IAP, after an analysis of published literature on prospective randomised controlled trials on the drug, had opined, "Nimesulide is as safe or unsafe as other anti-pyretic drugs." The IAP said that the drug can be prescribed for short-term use in children, for less than 10 days of treatment. Data on the effect of the drug in children below six months being limited, no definite conclusions could be drawn on the effect of such use, IAP told the DCGI.

Even as the controversy over the safety of the non-steroid anti-inflammatory drug (NSAID) nimesulide raged on, Dr Reddy's Labs (DRL)and Nicholas Piramal India, two of the leading manufacturers of this drug in India,- decided to withdraw some of their brands containing nimesulide from the market. DRL withdrew all fixed-dose combinations of nimesulide (Nise Spas and Nise Spas DS, Novigan N, NIAP and Nise MR) and Nicholas Piramal India withdrew its nimesulide tablets for adults from the market. Dr Reddy's Nise brand is the market leader in the nimesulide-based NSAID segment and is still available. Also available still is Nimulid, another leading brand marketed by Panacea Biotec, another leading manufacturer of this drug.

DCGI prayed that the matter be referred to the DTAB (Drug Technical Advisory Board) since it is the constitutional body with expertise on drugs. The DTAB (with 5 out of 10 members attending the meeting) informed the court that since "no adverse reports had been received from within the country," there was no need to ban the drug. On the specific question of use in children, the DCGI filed a false affidavit to say that its use in children was allowed in Switzerland and Belgium. The fact is that it was never permitted in these two countries. Social Jurist filed documents from the drug regulators of Belgium and Switzerland but the Delhi High Court ignored the submission. Ultimately the High Court refused to intervene, which meant that nimesulide could continue to be sold; and indeed it continues to be sold in the Indian markets..

On the question of nimesulide FDCs with other agents, the DCGI informed the Court that the FDCs were launched without its approval due to licences issued by state drug controllers; that FDCs with paracetamol or tizanidine or chlorzoxazone had been in the market for some time and were being patronised by the medical profession and no adverse reports had been received; hence they may be "regularised" (i.e., legally permitted post-facto). On other FDCs, the DTAB will be asked to review. So far, even after the lapse of more than three years, nothing has happened and new FDCs with three agents have been launched since.

Around May 2003, the Drugs Controller General of India (DCGI) directed nimesulide manufacturers to withdraw the paediatric "drops" formulation from the market. Those concerned at the turn of events felt that withdrawing drops alone and letting nimesulide suspensions off the hook would defeat the purpose of a ban. As the "drops" are only a diluted form of the suspension, why cannot the government ban the entire drug, these experts argued. By directing a ban on nimesulide drops, the DCGI did accept that the drug had serious side-effects. Based on the suggestions of the DTAB (Drug Technical Advisory Board), the DCGI also asked that manufacturers to print a cautionary note on the label or the package insert saying that "co-administration with other potentially hepatotoxic drugs should be avoided."

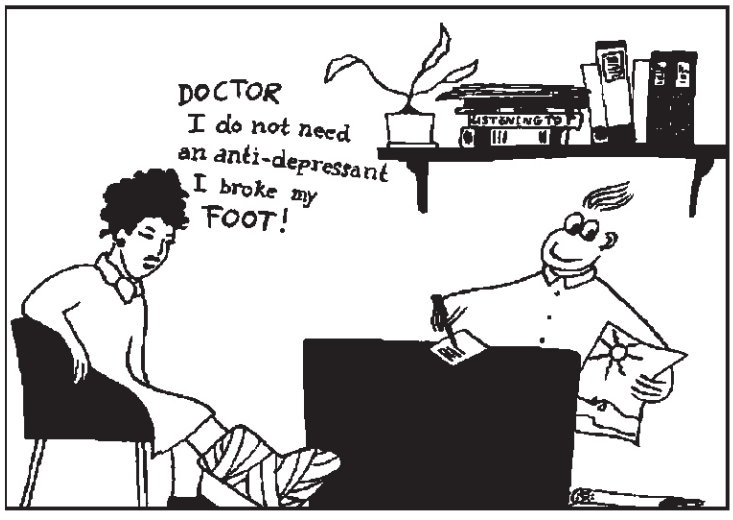
In a communication to the *Indian Journal of Pharmacology* (2003; 35: 121-122), "Nimesulide: The Current Controversy", authors V. Thawani, S. Sontakke, K. Gharpure, and S. Pimpalkhute wrote:

Most of the drug research is funded by the pharmaceutical industry. However let not the ADR monitoring be dictated by the manufacturers of the drug, suspected to cause ADR. If this does not happen, truthful reporting will never occur because of the vested interests of the powerful industry lobby. More disturbing is the influence, when an organized gang of 50 private practitioners opines in favour of the dangerous drug and their opinion is considered to let the drug thrive .... While the leading countries of the world have not allowed/ banned or withdrawn the drug, the opinion of a mere 50 private doctors has tilted the scale towards allowing the drug to continue to be marketed in India! It is also a matter of great sorrow that matters relating to serious and fatal ADRs of drugs are discussed in the media first and not in scientific bodies. Because we continue to miserably fail in taking a stand, the media continues to lead and beat us. No wonder that 50 organized private practitioners have succeeded in brainwashing those who finally matter …

Elsewhere *Current Science* ("Drugs control: A slippery slope", Vol. 83, No. 9, 10 Nov 2002) raised even more fundamental questions in its editorial:

The responsibility for ensuring, to the extent possible, the safety of widely used drugs rests with the Drugs Controller of India, whose office falls within the broad sphere of responsibility of the Ministry of Health. Does the Drugs Controller's office have the necessary wherewithal to make scientifically valid decisions on drugs? In an area whose technical complexity grows with each passing day, can an office functioning under a ministry, not noted for its scientific strengths, efficiently and credibly discharge its mandate? Can an office steeped in a 'ministerial culture' resist the pulls and pressures of competing pharmaceutical houses? The present attack on nimesulide and the publicity given to reports of its liver toxicity in children must undoubtedly have its origins in the strategic marketing wars that drug companies are prone to wage.

After all, the literature reports on the adverse reactions of nimesulide and other non-steroidal antiinflammatory agents have been known for some time. If there was reason for concern it is incumbent on the Drugs Controller to make these public, rather than to respond only when the popular press raises the issue, stridently. It is also necessary for manufacturers of nimesulide, particularly those with the muscle of research and development departments behind them, to provide convincing data that toxicity in local populations is not significant.



WHO EDM No 31, 2002

5. 5 Dexorange: a Top-Selling Anemia Preparation that used to Contain Haemoglobin[34]

An outstanding example of a patently irrational drug is that of Dexorange. This formulation is used for treatment of one of the most common and serious health problems of people, anemia. It is one of the top selling preparations in India with a Moving Annual Total in retail sales (ORG Nielsen Oct 2003) of Rs. 57 crores. Its overall rank in the top 300 brands was 16th in 2003 and it outperformed some of the rational preparations for treatment of anemia which do not even figure in the top 300 brands. Till 2000, this company, for over a decade and a half, was adding minute amounts of haemoglobin obtained from slaughterhouses under unhygienic conditions to its otherwise irrational formulation of iron.

The amount of haemoglobin added to the preparation was such as to provide a meager additional 2-3 mg of iron per 15 ml.

Ban on Haemoglobin Production

The Government today banned the production of fixed doses of haemoglobin, both natural and synthetic, in any form and also re-defined the term 'new-drug' by broadening its ambit.

Along with haemoglobin, the Centre also prohibited the manufacture of pancreatin or pancrelipase containing amylase, protease and lipase with any other enzyme. Explanation given by the Government for the above move was to weed out from the market irrational formulations/medicines which lack adequate therapeutic justification, i.e., drug combinations which have no rationality.

The products under these categories were examined by a 'Core Group' of technical experts and the recommendations of the core Group were reviewed by the Drugs Technical Advisory Board, a statutory body under the Drugs and Cosmetics Act, an official release issued by the Health Ministry said.

As far as redefining of the term 'new-drug' is concerned, the Government has decided to include "modern devices like new types of syringes, inter-dental brushes with anti-bacterial filament etc. and delivery systems like transdermal patches, implants under the skin etc., which are intended for internal and external use in the diagnosis, prevention, treatment etc., of diseases or disorders in human beings, will be covered within the definition of 'new drug' and will need to be approved by the Drug Controller of India, following the same procedure as is being followed for drugs," an official release issued by the Ministry said.

The amendment also covers the misuse of any new drug imported as a gift for the purpose of conducting clinical trials without specific permission of the Licensing Authority under Rule 21. This means that any import of new drug for purpose of clinical trial without due permission would be treated as a violation of the Drugs and Cosmetics Rules, even if the drug is received as a gift, and will attract the relevant penal provision, the release said.

The release stated haemoglobin obtained from animal blood could be unhygienic and such preparations are needed to be taken in extraordinary high volume to deliver the recommended level of iron in anaemic cases and thus lacks therapeutic rationale.

Similarly, pancreatin enzyme is prescribed only for the condition of pancreatic enzyme deficiency and therefore, addition of other enzymes does not have rationality, the release further said.

Source : *The Business Line*. August 24, 1999.

The addition of haemoglobin of animal origin to an iron preparation is without parallel in the pharmaceutical sector worldwide. No other formulary mentions it, and no other country allows it. How was this preparation passed for marketing in India? The answer is not clear. But it took years for the drug regulatory authorities to notice the irrationality of this top selling preparation and declare a ban on

haemoglobin preparations and wrote:

> *"haemoglobin obtained from animal blood could be unhygienic and such preparations are needed to be taken in extraordinary high volume to deliver the recommended level of iron in anemic cases and thus lacks therapeutic rationale."*

This particular preparation still contains an iron salt, which is less efficiently absorbed, in a concentration that is low, and is still marketed at a price that is extravagant. The cost of treating iron deficiency anemia with this preparation can be upto Rs. 600 per month, against the cost of a simple iron-folic acid preparation that should cost Rs 9 per month.

The case of the consistent marketing success of Dexorange is not a mere example but stands as a damning indictment of the state of affairs in the pharmaceutical sector, the government and the prescribers. It has put the interests of the voiceless patient/consumer in the background. If after more than a decade, during which this company marketed this top-selling preparation adding animal haemoglobin from slaughterhouse blood, the government finds that this addition was not justified, and in fact hazardous, why did it allow a preparation like this to be marketed in the first place? Are the drug regulatory authorities so deficient in scientific understanding that they cannot evaluate a simple preparation for anemia before approval? If they slipped up, why did it take a drug approved in 1971 to get banned in 2000, after 30 years of animal blood consumption by the unfortunate public of India?

5.6 Drugs Weeded Out

A series of drug combinations have been weeded out since 1980 by the Drugs Controller either as a result of the recommendations of the Drug Technical Advisory Board, or public pressure mounted through the Supreme Court and resulting court orders (see Annexure 3). Annexure 4 is a note on how to identify Harmful, Irrational and Useless Analgesics while Annexure 5 gives a list of Irrational Combinations of Paracetamol.

However, the resulting gazette notifications often tend to have a lot of loopholes, thus rendering the executive actions weak and ineffective. (See box *Banned Drugs: When is a Banned Drug not Banned in Effect*). For an excellent study of these notifications see Mira Shiva and Wishvas Rane. *Banned and Bannable Drugs* (Fifth Revised Edition). VHAI, New Delhi, August 2004.

GuidelinesforRationalUseofDrugs

- Prescribing a drug only when genuinely indicated
- Choosing drugs which are effective
- Using single-ingredient drugs
- Using drugs indicated for specific conditions
- Choosing drugs which are relatively safe
- Choosing cheaper alternatives

Some of the steps needed to rationalize the use of drugs in the market are:

- Elimination of new drugs, which are expensive and not necessary because other drugs with proven

efficacy already exist in the market.

- Elimination of useless, hazardous and harmful drugs which have irrational combinations.
- Use of Essential Drugs List.
- Marketing of drugs by their generic names.

Banned Drugs: When is a Banned Drug not Banned in Effect?

1. When the Government decides (in effect) to lift the ban, as in the case of clioquinol (di-iodohydroxyquinoline). Haemoglobin products were banned, unbanned and rebanned!

2. When the drug companies, who stand to lose from the ban, obtain a stay order on it and Government itself fails to vacate the stay order.

3. When the ban is diluted, so as to leave out some hazardous drugs.

The banning of steroid combinations excluded steroids intended for asthma. As a result steroid combinations previously indicated for other illnesses were suddenly recommended for asthma, while usage for earlier indications continued.

Fixed dose combinations of chloramphenicol were recommended for banning by DCGI in 1980. It was diluted by the DTAB to chloramphenicol combinations, excluding choloramphenicol and streptomycin combination.

4. When a ban order is ambiguously worded, leaving room for loopholes. The Gazette Notification of July 1983, failed to specify whether a drug would be banned only if all ingredients, or if any of the combination of ingredients, were present, e.g., yohimbine strychnine in testerone in tonic form.

Another example is the failure to specify the meaning of steroid combinations: as to whether it would include anabolic steroids and failure to give a listing of the specific drugs affected.

Wording the Gazette Notification in such a way that injectable preparation is left out when the preamble clearly states that the formulations are harmful and have no therapeutic value. But only oral dosage forms are mentioned in the section having legal status. Thus giving an impression that all formulations are banned (injectables and tablets) yet banning only the latter, e.g. the high dose oral formulation.

5. When the ban order is not enforced. When the legislation is inadequate, e.g., the earlier 22 categories of banned drugs could not be banned till the Drugs and Cosmetics Act was amended following which the Gazette Notification was issued in July 1983.

6. When the ban order is issued in a Gazette Notification and no effort is made to use the government media, e.g., AIR, Doordarshan as well as major national dailies to publicise the drugs and the brands involved.

7. When name of brands and the manufacturers of the banned drugs is not made public to prevent doctors from prescribing and consumers from consuming them.

8.When authorities concerned fail to ensure withdrawal of stocks from the manufacturers and the market.

9.When authorities concerned fail to seriously monitor the continued sale of banned drugs.

10. When authorities concerned consistently fail to punish those who violate the ban orders.

The Government of India had appointed in 1987, an Expert Committee on weeding out irrational/harmful/subtherapeutic drugs. It may be noted that the Government can ban not only hazardous drugs but under Section 26 A of the Drugs and Cosmetics Act 1940, the Government can ban drugs that do not have the "therapeutic value claimed for them or contain ingredients and in such quantity for which there is no therapeutic justification."

Source: Excerpted from, Mira Shiva and Wishvas Rane. *Banned and Bannable Drugs*. VHAI, New Delhi, 2004, pp 122 ff.[35]

EthicsofDrugUseforDoctors

1) Prescribe strictly rationally and promote rational therapy on all occasions, personal and professional.

2) Prescribe only essential, generic drugs, that are single ingredient formulations with accepted exceptions of combination drugs like co-trimoxazole, ORS, etc.

3) When two or more equivalent drugs are available for the same condition, prescribe the less costlier and safer alternative. Thus minimise use of liquids, injections and IVs.

4) When not sure of the dosage, mechanism or side-effects, consult standard textbooks and/or journals.

5) Update your knowledge by reading relevant scientific journals, and by promoting discussion of clinical experiences of rational therapy in appropriate professional forums. (Points 4 & 5 mean conscious investment of time and money).

6) Explain to the patient clearly how he/she has to take the drug. Encourage your patient to ask questions about the therapy and the mode of treatment. Respect the autonomy of the patient. And encourage his/her self-reliance.

7) Do not take, and if possible actively oppose, taking of, bribes, gifts, etc. from drug companies or going for seminars and trips sponsored by drug companies. It all adds to the cost of the drug to the end user apart from biasing your prescription in favour of the drug company's products.

8) Look out for adverse drug reactions; record and report the same to ADR (Adverse Drug Reaction Centres) centres in India and in relevant professional journals.

9) Avoid cut practice and poly therapy. Keep X-rays, lab tests and other such investigations to the minimum. If possible oppose publicly cut practice and poly therapy.

10) Above all innovate by using your clinical judgment. Most patients, especially from rural areas, will not be able easily to come back to you (if you are an urban practitioner for instance). See how you can make your client well in one trip and if possible with one or two drugs. Remember getting ill and getting well are socio-medical processes.

Sir William Osler: *A doctor at the beginning of his/her career starts with 20 drugs for one disease, and the one at the end of his/her career has one drug for 20 diseases.*

Annexure1

Why Some Leading Drugs in the Indian Market should not be sold - but are still sold

1) Fixed Dose Combinations (FDCs) of Antibiotics and or Antimicrobials

a) FDCs of Ampicillin and Cloxacillin

Comments:

(i) Both combinations belong to same class namely penicillins acting at the same site by same mechanism offering no synergism.

(ii) Claims like cloxacillin binds to penicillinase and makes it inactive are false.

(iii) No broader spectrum of action as claimed.

(iv) Fixed ratio of drugs does not allow flexibility of changing one or other antibiotic.

Recommendations: Ban all the formulations of ampicillin with cloxacillin in all types of formulations. Concurrently they could be used in appropriate doses where necessary.

b) FDCs of Amoxicillin and Cloxacillin

Brand name examples: Hipenox caps (Cadila); Megamox-500 caps (Max);

Novaclox (Cipla) caps, tabs, injections; Tresmox caps (Sarabhai); Tormoxin plus and Twiciclox (Torrent) and other such.

Comments:

All above arguments for ampicillin and cloxacillin combinations hold in this case also, in addition to the following: dosing pattern of both these antibiotics is different as mentioned in standard medical textbooks: amoxicillin is recommended three times a day whereas cloxacillin is recommended four times a day, thus creating a discrepancy in dosing time schedules.

Recommendations: As above for FDCs of ampicillin and cloxacillin: to be weeded out and can be used concurrently if necessary.

c) FDCs of Metronidazole/Tinidazole plus Diloxanide Furoate/Di-iodohydroxyquinoline (DHQ) combinations

Brand Name Examples: Dinite (Searle) tabs, suspension; Entamizole (Boots) tabs, syrup; Flagyl-DF (Rhone-Poulenc) tabs; Metrogyl compound (Unique) tabs; Qugyl (Searle) tabs, suspension; Cyloxanid (Biddle-Sawyer) tabs; Wotinex (Wockhardt) tabs; Zoa Forte (Tata-Pharma) tabs and such others.

[2]Some brand names given may have changed since1993 when this was submitted to the Supreme Court of India as part of a petition but the situation is substantially the same. Where the group of drugs no longer exist, it is mentioned.

Comments:

(i) Metronidazole and tinidazole are tissue amoebicides whereas diloxanide furoate and DHQ are luminal amoebicides.

(ii) The standard treatment of invasive amoebiasis is tab. metronidazole (35 to 50 mg/kg/day in the three divided doses) for 7-10 days followed by diloxanide furoate 500 mg three times a day for further 10 days.

(iii) According to Goodman and Gillman (1990) for asymptomatic and non-invasive intestinal amoebiasis, only diloxanide furoate is sufficient. In such patients these combinations will lead to unnecessary intake of metronidazole/tinidazole. In case of invasive intestinal and systemic amoebiasis, including amoebic diseases, metronidazole/tinidazole is given followed by diloxanide furoate (Goodman-Gillman, p.955).

(iv) According to Laurence D.R (*Clinical Pharmacology,* 1992) treatment for tissue amoebiasis should always be followed by a course of luminal amoebicide to eradicate the source of the infection (p.207).

(v) The combination is recommended nowhere.

Recommendations: Ban all these combinations. Let these drugs be separately available for their appropriate use.

d) FDCs of Metronidazole/Tinidazole and Furazolidone

Brand Name Examples: Flagyl F (Rhone Poulenc) tabs, suspension; Fumedil-DS (Ethnor) caps; Kaltin-MF(Abbott) suspension; Metrogyl-F (Unique) tabs, suspension; Tini-F syrup (Kopran) and such other products.

Comments:

(i) Metronidazole is primarily an antiamoebic whereas furazolidone is an antibacterial effective against colonic gram negative bacteria. Furazolidone is nowhere mentioned for use in the latest editions of Goodman Gillman (1990) and *Clinical Pharmacology* by D.R. Laurence (1992). They are perhaps replaced by safer and more effective agents.

(ii) All diarrhoeas/dysenteries are not polymicrobial in origin - not always due to concurrent infection by E.histolytica and colonic pathogenic bacteria. Thus a person suffering from amoebiasis is condemned to take furazolidone and a patient suffering from bacterial dysentery has to take metronidazole/tinidazole unnecessarily. This increases cost of therapy and chances of ADR.

(iii) Most diarrhoeal diseases do not need treatment with antibiotics/antibacterials. Many of them are self-limiting and need only supportive therapy like fluids and electrolytes with ORS.

Recommendations: Ban all formulations containing metronidazole/tinidazole and furazolidone combinations. They may be separately formulated and marketed in appropriate conditions.

2. FDCs of Analgesics with Analgesics/Antiinflammatory drugs

FDCsofIbuprofen/Ketoprofen/DiclofenacwithParacetamol/Analginandsuchothers

Brand Name Examples: Combiflam (Roussel) tabs and suspension; Ibugesic Plus (Cipla) tabs, susp.; Lederflam Plus (Lederle) tabs; Magadol (Alembic) tabs, suspension.; Tribusynth (Astra-IDL) tabs; Zupar (Allenburys) caps, tabs, syrup; Ketonal-D (PCI); Redufin-A (Unique); Cofenac (Protec) tabs; Diclogesic (Torrent) tabs; Diclofam Plus (Max) tabs; Fenaside-P (Nicholas) tabs; and such others.

Comments:
i) Ingredients of all these combinations, mainly paracetamol, analgin, ibuprofen, diclofenac, etc., belong to a single category of drugs, i.e., Non-Steroidal Inflammatory Drugs (NSAIDS). Paracetamol and analgin have chiefly analgesic and antipyretic actions. Ibuprofen and diclofenac have mainly anti-inflammatory action in addition to having analgesic and antipyretic effects. All these effects are produced by inhibition of synthesis of prostaglandins. Since the mechanism of action is same, there is no synergism. More over anti-inflammatory action leads to pain relief.

ii) NSAID combinations are known to cause direct damage to kidney (*Clinical Pharmacology*, Laurence, 1992, p.469.) Although nephropathy is uncommonly associated with the long-term use of individual aspirin-like drugs, the abuse of analgesic mixtures has been linked to the development of renal injury including papillary necrosis and chronic interstitial nephritis (Goodman-Gillman, 1990, p.643).

Recommendations: All such combinations should be banned. Individual ingredients, except analgin, however may be marketed for use either singly or concurrently in appropriate doses in suitable conditions.

ii) Safer and better alternatives, including injections, for analgin are available. Looking to the dreaded ADR of analgin on bone marrow, its marketing as single agent or combination should be banned.

3) Iron Preparations

Haemoglobincontainingironpreparations(bannedsince2000)

Brand Name Examples: Bio-syn (Gufic) liquid; Dexorange Plus (Franco-Indian) caps and syrup; Globac (Alidac) caps and liquid; Haem Up (Cadila) liquid and gems; Hb-Rich (Merind) liquid; Probofex with Haemoglobin (Wockhardt) syrup; Reditone Plus (Blue Cross) liquid; and several such others.

Comments:

(i) The source of haemoglobin is blood of animals killed in slaughter houses. This could be dangerous for human use for the fear of causing allergic reactions (foreign proteins), transmission of infections (zoonosis, because blood is a rich medium for bacterial growth), etc.

(ii) Haemoglobin per se is a poor source of elemental iron absorbed by the body. More than half a bottle of any of above preparations will be required for appropriate response in anaemic conditions.

(iii) Because of lack of this knowledge on part of patients, and even doctors, it will result in subtherapeutic use and inadequate treatment.

(iv) A six-month course with such preparations will cost approx. Rs.3,650/- as against Rs.55/- (approx.) of treatment with nearly rational preparations of iron-folic acid (Macrofolin-Iron of Glaxo) available in the market.

(v) No standard textbooks of medical sciences or medical journals mention the use of haemoglobin as a drug.

Recommendations: (i) Totally ban the use of iron preparations containing haemoglobin from any source.

(ii) Only preparations containing iron and folic acid (in appropriate amounts) are rational and recommended by WHO. Only such preparations need to be allowed.

4) Cough Suppresants, Expectorants and Mucolytics

Combinations containing so-called expectorants like iodides, chlorides, bicarbonates, acetates, squill, guiaphenesin, creosotes and volatile oils in addition to central cough suppressants, antihistaminics, bronchodilators and mucolytics.

Brand Name Examples: Alex cough formula (Lyka) liquid; Asthalin expectorant (Cipla) syrup; Benadryl cough formula (Parke-Davis) syrup; Bro-Zedex (Wockhardt) syrup; Clistin-DMR (Ethnor) liquid; Contac-CC (Smith-Kline Beecham) tab; Coscopin-Linctus (Biological-E) syrup; Detigen linctus (Bayer) liquid; Dilosyn expectorant (Allenburys) liquid; Dristan Expectorant (Manners) liquid; Piriton expectorant (Glaxo) liquid; Polaramine expectorant (Fulford) syrup; Zeet expectorant (Alembic) syrup; and many such others.

Comments:

(i) Cough is a protective reflex of body, often a symptom of many common and self-resolving conditions like common cold.

(ii) Cough could be productive or unproductive. When unproductive and discomforting to patients, it could be suppressed by centrally acting antitussives like codeine, noscapine, or dextromethorphan.

(iii) When cough is due to allergic reasons, it can be tackled by giving H1 antagonists; when due to bronchospasm, it can be relieved by giving bronchodilators like salbutamol or terbutaline.

(iv) When the cough is productive, it should be encouraged for the purpose of expectoration. Expectorants like iodides, chlorides, guiaphenesin, creosotes, volatile oils, etc., are claimed to have expectorant value but *may have no more than placebo value* (Laurence, p.506). Expectorants given in effective doses are often not tolerated and produce ADR. *Water inhalation as an aerosol, though cheap,is not to be despised. Simply hydrating a dehydrated patient can have a beneficial effect in lowering sputum viscosity* (Laurence, p.505).

(v) Most expectorants are of unproven value as per standard Indian textbooks like *Pharmacology and Pharmacotherapeutics* (Satoskar, 1995, pp.308-309) and *Textbook of Pharmacology* (K.D.Tripathy, 3rd Edition, 1994).

(vi) The Model List of Drugs (Seventh List, WHO, 1992) has not mentioned any substance except centrally acting cough suppressants in the category of drugs for cough.

(vii) Water in the vapour form is the best expectorant according to Harrison's Textbook of Medicine.

(viii) Using expectorants is a costlier way of helping a condition which is often self-resolving.

Recommendations: (i) Preparations containing only centrally acting cough suppressants as single ingredient should be made available.

(ii) Bronchodilators may be allowed to be combined with mucolytics but nothing else.

(iii) Single ingredient preparations of antihistamines may be permitted for allergic cough.

(iv) There is no need for any expectorants in present day therapeutics. Ban all preparations of expectorants.

5) Oral Enzymes and Digestives

a) Oral Enzymes for proteolytic and anti-inflammatory action, i.e., trypsin, chymotrypsin, serratipeptidase, etc.

Brand Name Examples: Alfapsin (Lyka) tabs; Chymoral Forte (Elder) and Chymoral Forte D.S. (Elder) tabs; Restochyme (Walter- Bushnell) tabs; Bidanzen Forte (Biddle-Sawyer) tabs; Kineto (Systopic) tabs; Seraini (AFD) tabs and several such others.

Comments:(i) The only indication for alpha-chymotrypsin approved by FDA in U.S.A. is for topical use in eye following surgery.

(ii) These enzymes are protein in nature and when given orally are digested by pepsin in the stomach, rendering then ineffective. Even if they are protected from action of gastric juice, there is no evidence to show that they reach the site of infection to produce beneficial actions.

(iii) No pharmocokinetic and bio-equivalence studies of these preparations are available.

(iv) These enzyme preparations are not mentioned in standard textbooks of medicine.

(v) Being of animal origin they may produce allergic effects.

(vi) They are too expensive, especially for non-indications.

Recommendations: All these products must be banned forthwith.

b) Oral Digestive Enzyme Preparations of Pancreatin, Diastase and Takadiastase, Papain, etc.*

Brand Name Examples: Aristozyme (Aristo) caps, drops, liquid; Bestozyme (Biological-Evans) caps, syp, paediatric syrup; Digiplex (Rallis), all preparations; Essentiale (Rhone-Poulenc) caps; Festal (Hoechst) tabs; Merizyme (Mercury) syrup; Neopeptine (Raptakos) caps. drops, syrup; Paptazyme (AFD) tabs; Takazyme (Parke-Davis) powder; Unienzyme (Unichem) tabs, drops; Vitazyme (East India) liquid, drops; Vizylac (Unichem) caps, dry syrups; and several such others.

Comments: (i) Digestants are drugs that supposedly promote the process of digestion in the gastrointestinal tract in conditions characterised by a lack of one or more of the specific substances that function in the digestion of food. Although a number of products are marketed including many bizarre mixtures of components, the only preparations that merit consideration are those of pancreatic enzymes.

*Fixed dose combinations of Pancreatin or Pancrelipase containing amylase, protease and lipase with any other enzyme. are banned since September 1, 2000.

(ii) These preparations are employed for the treatment of conditions in which the secretion of pancreatic juice is deficient, for instance, pancreatis and mucoviscidosis (Goodman-Gillman, 1990, p.929)

(iii) Acid and peptic activity in the stomach can destroy the pancreatic enzymes. Enteric coating may prevent delivery of enzymes in the duodenum (Goodman-Gillman, 1990, p.929).

(iv) Only one tenth of the normal pancreatic output is sufficient to prevent excess fat or nitrogen loss. They are preparations of animal origin and of variable potency. Many of these drugs have been tested for specific effect in acute pancreatis and none has shown convincing benefit (Laurence, 1992, p.546)

(v) Many of the ingredients present in the above cited formulations in India, are not mentioned in standard textbooks of medicine and pharmacology.

(vi) Mucoviscidosis is an uncommon condition in India.

(vii) These are unnecessary and costly preparations. Essential drug list of WHO (1992) has not mentioned any of these preparations.

Recommendations: All these formulations of oral digestive enzymes should be banned immediately with the following exception: only enteric coated preparations of pancreatic enzymes may be allowed for restricted use in properly diagnosed cases of pancreatis and mucoviscidosis under expert supervision.

6) Local Antiseptics

Various Preparations of Povidone Iodine, i.e., solutions, mouth washes, scrubs, skin ointments/creams, vaginal pessaries, etc.

Brand Name Examples: Alphadine (Nicholas) mouth wash solution, vaginal pessaries, ointment; Betadine (Win-Medicare) mouth wash solution, pessaries, ointment, scrub; Wokadine (Wockhardt) solution, pessaries, ointment, powder, gargle, scrub; Piodin (Croydon) solution, cream, mouth wash; Povidax (Unique) solution, mouth wash; Torvidone (Torrent) solution, cream; and several such others. (Though fixed dose combination of Pancreatin or Pancrelipase containing amylase, protease and lipase with any other enzyme are banned since 2000, some of the combinations mentioned here are still available.)

Comments:

(i) Povidone-iodine is an iodophore, a loose complex of iodine with poly-vinyl-pyrrolidone. A 10 percent solution is a stable one and when diluted 10 to 100 times with water, it sets iodine in free form which is effective as a germicidal. After such dilution, activity of povidone-iodine increases 10 fold (which is still only 1/15th of the activity of 2 percent tincture of iodine.) [Goodman-Gillman, 1985, 7th edition].

(ii) Considering the above facts:

* Formulations like vaginal pessaries and ointments will be useless.
* Solutions, scrubs, etc., should be appropriately diluted. However, the instruction on bottles say "use full strength" or do not advise about dilution. This leads to colossal wastage of anti-septic solution without the desirable anti-septic effect.

Recommendations: (i) Ban preparations like creams, ointments, pessaries. (ii) Allow the formulations like

scrubs and solutions in appropriate strength, that is, 10 percent, with clear cut instructions on its use, that is dilute with water by 10 to 100 times before use.

In addition to the above, the following categories of drugs also need to be banned/rationalised:

7) FDCs of Antiasthmatic Drugs

8) FDCs of Antacids

9) Lactobacillus Preparations

10) Topical Anticoagulants

11) Oral/Injectable Haemostatics except Vitamin K

12) Cerebral Activators such as Pyritinol and Piractecam (Torrent)

13) Cerebral Vasodilators

14) Placentrex (Albert David) and products based on human/animal placenta

15) Ginseng and other such so-called sexual rejuvenators

16) Presence of Alcohol not required as solvents

17) Entire categories of products under the so-called label of Nutritional Supplements.

18) Drugs (of non-modern medical systems) approved by the FDA purporting to cure snake bites, increase semen, increase the risk of abortion, increase fertility, brain tonics, etc.

Source*: Additional Affidavit of LOCOST in Supreme Court Writ Petition No.698/93, Drug Action Forum and ors*

Annexure2

Partial, Cumulative List of Dubious Fixed-Dose Combinations (FDCs) Being Marketed in India: But not Approved in Any Developed Country. Most of these Combinations are not Approved by the Drugs Controller General, India and hence Illegal.[36]

Alprazolam + Sertraline
Alprazolam + Imipramine
Alprazolam + Fluoexetine
Alprazolam + Melatonin
Imipramine + Diazepam
Risperidone + Trihexyphenidyl
Norfloxacin + Tinidazole
Norfloxacin + Tinidazole + Dicyclomine
Norfloxacin + Tinidazole + Loperamide
Norfloxacin + Metronidazole
Norfloxacin + Ornidazole
Ciprofloxacin + Tinidazole
Ciprofloxacin + Metronidazole
Ofloxacin + Tinidazole
Ofloxacin + Metronidazole
Ofloxacin + Ornidazole
Fluconazole + Tinidazole
Doxycycline + Tinidazole
Tetracycline + Metronidazole
Mefenamic Acid + Drotaverine
Nimesulide + Paracetamol
Nimesulide + Diclofenac
Nimesulide + Dicyclomine
Nimesulide + Chlorzoxazone
Nimesulide + Methocarbamol
Nimesulide + Camylofin
Nimesulide + Serratiopeptidase
Nimesulide + Tizanidine

Nimesulide + Paracetamol + Chlorzoxazone
Nimesulide + Tizanidine + Paracetamol
Rofecoxib + Tizanidine
Ibuprofen + Tizanidine
Diclofenac + Tizanidine
Diclofenac + Famotidine
Diclofenac + Paracetamol + Tizanidine
Diclofenac + Serratiopeptidase
Diclofenac + Paracetamol + Serratiopeptidase
Ibuprofen + Paracetamol + Magnesium Trisilicate
Ranitidine + Dicyclomine
Sucralfate + Oxethazine
Cisapride + Simethicone
Cisapride + Omeprazole
Mosapride + Methylpolysiloxane
Magaldrate + Simethicone + Oxethazine + Dicyclomine
Diazepam + Dried Alum. Hydrox. Gel + Alum. Glycinate + Oxyphenonium
Diazepam + Dried Alum. Hydrox. Gel + Mag. Trisilicate + Dimethylpolysiloxane
Diazepam + Magaldrate + Oxyphenonium
Diazepam + Propantheline + Dihydroxy. Alum.
Amoxycillin + Serratiopeptidase
Pipenzolate + Phenobarbitone
Amoxycillin + Probenecid + Tinidazole
Cefuroxime + Serratiopeptidase
Roxithromycin + Ambroxol
Ciprofloxacin + Ambroxol
Cefoperazone + Sulbactum
Ramipril + Losartan
Amlodipine + Lisinopril
Amlodipine + Enalapril
Amlodipine + Ramipril
Amlodipine + Losartan
Atenolol + Alprazolam
Propranolol + Alprazolam
Propranolol + Diazepam
Cinnarizine + Domperidone
Domperidone + Ranitidine
Domperidone + Omeprazole
Domperidone + Famotidine
Mebendazole + Pyrantel
Mebendazole + Levamisole
Simvastatin + Nicotinic Acid
Cetirizine + Paracetamol + Phenylpropanolamine

Annexure3

List of Drugs Prohibited for Manufacture and Sale through Gazette Notifications[37]

1. Amidopyrine.
2. Fixed dose combinations of vitamins with anti-inflammatory agents and tranquilizers.
3. Fixed dose combinations of Atropine in Analgesics and Antipyretics.
4. Fixed dose combinations of Strychnine and Caffeine in tonics.
5. Fixed dose combinations of Yohimbine and Strychnine with Testosterone and Vitamins.
6. Fixed dose combinations of Iron with Strychnine, Arsenic and Yohimbine.
7. Fixed dose combinations of Sodium Bromide/chloral hydrate with other drugs.
8. Phenacetin.
9. Fixed dose combinations of antihistaminic with anti-diarrhoeals.
10. Fixed dose combinations of Penicillin with Sulphonamides.
11. Fixed dose combinations of Vitamins with Analgesics.
12. Fixed dose combinations of any other Tetracycline with Vitamin C.
13. Fixed dose combinations of Hydroxyquinoline group of drugs with any other drug except for preparations meant for external use.
14. Fixed dose combinations of Corticosteroids with any other drug for internal use.
15. Fixed dose combinations of Chloramphenicol with any other drug for internal use.
16. Fixed dose combinations of crude Ergot preparations except those containing Ergotamine, Caffeine, analgesics, antihistamines for the treatment of migraine, headaches.
17. Fixed dose combinations of Vitamins with Anti-TB drugs except combination of Isoniazid with Pyridoxine Hydrochloride (Vitamin B6).
18. Penicillin skin/eye Ointment.
19. Tetracycline Liquid Oral preparations.
20. Nialamide.
21. Practolol.
22. Methapyrilene, its salts.
23. Methaqualone.
24. Oxytetracycline Liquid Oral preparations.
25. Demeclocycline Liquid Oral preparations.
26. Combination of anabolic Steroids with other drugs.
27. Fixed dose combination of Oestrogen and Progestin (other than oral contraceptive) containing per tablet estrogen content of more than 50 mcg (equivalent to ethinyl estradiol) and progestin content of more than 3 mg (equivalent to norethisterone acetate) and all fixed dose combination injectable preparations containing synthetic Oestrogen and Progesterone. (Subs. By Noti. No. 743 (E) dt 10-08-1989)
28. Fixed dose combination of Sedatives/ hypnotics/anxiolytics with analgesics-antipyretics.
29. Fixed dose combination of rifampicin, isoniazid and pyrazinamide, except those which provide daily adult dose given below:

Drugs	Minimum	Maximum
Rifampicin	450 mg	600 mg
Isoniazid	300 mg	400 mg
Pyrazinamide	1000 mg	1500 mg

30. Fixed dose combination of Histamine H-2 receptor antagonists with antacids except for those combinations approved by Drugs Controller, India.
31. The patent and proprietary medicines of fixed dose combinations of essential oils with alcohol having percentage higher than 20% proof except preparations given in the Indian Pharmacopoeia.
32. All Pharmaceutical preparations containing Chloroform exceeding 0.5% w/w or v/v whichever is appropriate.
33. Fixed dose combination of Ethambutol with INH other than the following: INH/Ethambutol 200 mg./ 600 mg. 300 mg./ 800 mg.
34. Fixed dose combination containing more than one antihistamine.
35. Fixed dose combination of any anthelmintic with cathartic/purgative except for piperazine/Santonim.
36. Fixed dose combination of Salbutamol or any other bronchodilator with centrally acting anti-tussive and/or antihistamine.
37. Fixed dose combination of laxatives and/or anti-spasmodic drugs in enzyme preparations.
38. Fixed dose combination of Metoclopramide with systemically absorbed drugs except fixed dose combination of metoclopramide with aspirin/paracetamol
39. Fixed dose combination of centrally acting, antitussive with antihistamine, having high atropine like activity in expectorants.
40. Preparations claiming to combat cough associated with asthma containing centrally acting antitussive and/ or an antihistamine.
41. Liquid oral tonic preparations containing glycerophosphates and/or other phosphates and/or central nervous system stimulant and such preparations containing alcohol more than 20% proof.
42. Fixed dose combination containing Pectin and/or Kaolin with any drug which is systemically absorbed from GI tract except for combinations of Pectin and/or Kaolin with drugs not systemically absorbed.
43. Chloral Hydrate as a drug.
44. Dovers Powder I.P.
45. Dover's Powder Tablets I.P.
46. Antidiarrhoeal formulations containing Kaolin or Pectin or Attapulgite or Activated Charcoal.
47. Antidiarrhoeal formulations containing Phthalyl Sulphathiazole or Sulphaguanidine or Succinyl Sulphathiazole.
48. Antidiarrhoeal formulations containing Neomycin or Streptomycin or Dihydrostreptomycin including their respective salts or esters.
49. Liquid Oral antidiarrhoeals or any other dosage form for pediatric use containing Diphenoxylate Lorloperamide or Atropine or Belladona including their salts or esters or metabolites Hyoscyamine or their extracts or their alkaloids.
50. Liquid Oral antidiarrhoeals or any other dosage form for pediatric use containing halogenated hydroxyquinolines.
51. Fixed dose combination of antidiarrhoeals with electrolytes.
52. Patent and Proprietary Oral Rehydration Salts other than those conforming to the WHO formula.
53. Fixed dose combination of Oxyphenbutazone or Phenylbutazone with any other drug.

54. Fixed dose combination of Analgin with any other drug.
55. Fixed dose combination of Dextropropoxyphene with any other drug other than anti-spasmodics and/or non-steriodal anti-inflammatory drugs (NSAIDS).
56. Fixed dose combination of a drug, standards of which are prescribed in the Second Schedule to the said Act with an Ayurvedic, Siddha or Unani drug.
57. Mepacrine Hydrochloride (Quinacrine and its salts) in any dosage form for use for female sterilization or contraception.
58. Fenfluramine and Dexfenfluramine.
59. Fixed dose combination of Diazepam and Diphenhydramine Hydrochloride.
60. Fixed dose combination of Metoclopramide with other drugs except combination of metoclopramide with aspirin/paracetamol (wef Sep 1, 2002)

DRUGS PROHIBITED FOR MANUFACTURE, SALE AND DISTRIBUTION FROM SUBSEQUENT DATE

	Drug/Formulation	Effective date	Notification
1.	Cosmetics Licensed as toothpaste/tooth powder containing tobacco.	With immediate effect	GSR 444(E) dt.30.4.92
2.	Parenteral Preparations fixed dose combination of streptomycin with Penicillin	Jan 1, 1998	GSR 93(E) dt.25.2.97
3.	Fixed dose combination of Vitamin B1, Vitamin B6 and Vitamin B12 for human use	Jan 1, 2001	GSR 702(E) dt.14.10.99
4.	Fixed dose combination of haemoglobin in any form (natural or synthetic).	Sep 1, 2000	GSR 814(E) dt.16.12.99
5.	Fixed dose combination of Pancreatin or Pancrelipase containing amylase, protease and lipase with any other enzyme.	Sep 1, 2000	GSR 814(E) dt.16.12.99
6.	Fixed dose combination of Nitrofurantoin and trimethoprim	Jan 1, 2002	GSR 170(E) dt.12.3.01
7.	Fixed dose combination of Phenobarbitone with any anti-asthmatic drugs	Jan 1, 2002	GRS 170(E) dt.12.3.01
8.	Fixed dose combination of Phenobarbitone with Hyoscin and/or Hyoscyamine	Jan 1, 2002	GSR 170(E) dt.12.3.01
9.	Fixed dose combination of Phenobarbitone with Ergotamine and/or Belladona	Jan 1, 2002	GSR 170(E) dt.12.3.01
10.	Fixed dose combination of Haloperidol with any anti-cholinergic agent including Propantheline Bromide.	Jan 1, 2002	GSR 170(E) dt.12.3.01
11.	Fixed dose combination of Nalidixic Acid with any anti-amoebic including Metronidazole	Jan 1, 2002	GSR 170(E) dt.12.3.01

	Drug/Formulation	Effective date	Notification
12	Fixed dose combination of Loperamide Hydrochloride with Furazolidone	Jan 1, 2002	GSR 170(E) dt.12.3.01
13	Fixed dose combination of Cyproheptadine with Lysine or Peptone.	Jan 1, 2003	GRS 170(E) dt.12.3.01
14	Astemizole	Apr 1, 2003	GSR 191(E) dt.5.3.03
15	Terfinadine	Apr 1, 2003	GSR 191(E) dt.5.3.03
16	Fenformin	Oct 1, 2003	GSR 780(E) dt.1.10.03
17	Rofecoxib and its formulations for human use	Dec 13, 2004	
18	Valdecoxib and its formulations for human use	July 25, 2005	GSR 510 (E)

Annexure4

Identification of Harmful, Irrational and Useless Analgesics

Analgesics are the most widely used OTC medicines and the market is flooded with lots of analgesics available in single as well as combination forms. All of these available products are not useful, and hence it is very important for the consumer to identify the harmful, irrational and useful analgesics and choose the right product for his/her condition.

The following information will give a brief account of the analgesics which should not be used as they offer no special benefits over the rational analgesic product.

I Analgesics that are harmful

a) Analgin (Dipyrone) and its combinations

The use of Analgin and its combinations can cause severe blood disorders, the appearance of which is sudden and unpredictable. The risk of such serious adverse effects of analgin and the availability of other safer and equally effective analgesics (e.g., aspirin, paracetamol) do not justify the use of analgin. It has been banned in many countries all over the world. Examples of brand products of Analgin (single and combination) are listed below:

Brand	*Content*	*Manufacturer*
Novalgin	Analgin	Hoechst
Baralgan	Analgin + Pitofene + Fenpivenium broncide	Hoechst

Analgin	Analgin	IDPL
Ultragin	Analgin + Paracetamol + Caffeine	Wyeth

Baralgan has been since banned by an order of the Supreme Court of India.

FDCs of analgin are now banned.

b) Oxyphenbutazone and Phenylbutazone

The use of oxyphenbutazone and phenylbutazone as anti-inflammatory drugs is restricted to only hospital treatment of severe conditions like ankylosing spondylitis.

They cause serious adverse effects such as peptic ulcer, blood disorders, kidney and liver problems, and hence their use for minor inflammatory ailments is not recommended. They have been banned in many countries all over the world and safer alternatives such as aspirin, paracetamol and ibuprofen are being recommended. Examples of brand products of oxyphenbutazone and phenylbutazone (single and combination) are:

Brand	*Content*	*Manufacturer*
Actimol	Phenylbutazone + Paracetamol	Pharmed
Algesin	Phenylbutazone + Lidocaine	Alembic
Zolandin	Phenylbutazone	S.G. Pharma
Zolandin Alka.	Phenylbutazone + Dried Alum.Hydrox. gel + Mg. Trisilicate	S.G.Pharma
Phenabid	Oxyphenbutazone	IDPL
Reparil	Oxyphenbutazone	F.D.C.
Butadex	Oxyphenbutazone + Chloroquine Phos.	Cadila
Flumar - P	Oxyphenbutazone + Paracetamol	Indoco
Tromalgio	Oxyphenbutazone + Analgin	La Pharma

II Irrational Analgesic Combinations

a) Analgesics plus Caffeine: This combination unnecessarily increases the cost of the product. Beside caffeine has got no analgesic or anti-inflammatory effect and it may itself induce headache in excess doses or on sudden stopping of the medicine. Examples of marketed products are:

Brand	*Contents*	*Manufacturer*
Micropyrin	Aspirin + Caffeine	Nicholas
Zimalgin	Analgin + Paracetamol + Caffeine	Rallis

b) Analgesics plus Metoclopramide: In these products metoclopramide is claimed to help produce a more rapid effect by facilitating the absorption of analgesics. However, this is not true. Moreover, metoclopramide causes serious adverse effects like drowsiness, fatigue, etc. Hence this combination is useless, irrational and expensive. Examples of marketed products are:

Brand	*Contents*	*Manufacturer*
Motopar	Paracetamol + Metoclopramide	CFL Pharma
Paramet	Paracetamol + Metoclopramide	Wallace

FDCs of metoclopramide with other drugs except combination of metoclopramide with aspirin/paracetamol have been banned in India from September 2002.

c) Analgesics plus Sedatives: This combination can cause excessive sedation (sleeping effect) which can be dangerous. Hence it is an irrational and expensive combination. Examples of marketed products are:

Brand	*Contents*	*Manufacturer*
Pomagin	Analgin + Diazepam	Alkem
Walagesic	Dextropropoxyphene + Paracetamol + Diazepam	Wallace
Proxyron	Dextropropoxyphene + Paracetamol	Wockhardt

III Useless Analgesics

a) Enzymes and Chymotrypsin as Anti-inflammatory Agents: Although available in the market, the use of chymotrypsin and other enzymes in the treatment of swelling and pain has not been proven adequately. Examples of marketed products are:

Brand	*Contents*	*Manufacturer*
Alfapsin	Alpha Chymotrypsin with 1ml Sodium Chloride Injection (for use in cataract Surgery)	Ranbaxy

Annexure 5

Irrational Combinations of Paracetamol[38]

Since paracetamol is a very commonly used drug, we briefly discuss here the rationality of formulations available which contain paracetamol.

1. Combined formulations of paracetamol with NSAIDs

Combination of paracetamol with any NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) can be justified on the basis that NSAIDs possess anti-inflammatory activity which is lacking in paracetamol. However, anti-inflammatory activity is required in inflammatory conditions like various types of arthritis. In such cases anti-inflammatory property itself relieves the pain, so, paracetamol has no role and combination is irrational. Furthermore, NSAIDs like phenylbutazone are banned and so is the combination. On the other hand NSAIDs like ibuprofen and indomethacin also possess antipyretic property thus no additional benefit occurs when such combination are used. Moreover, combinations of NSAIDs are more likely to produce nephropathy as compared to single agent.

2. Combinedformulationsofparacetamolwithanalgesics

Paracetamol itself is an analgesic. So combination with other analgesics is irrational. Such combinations have not been proved superior to either of the drugs except when paracetamol combined with an opioid like codeine or dextropropoxyhphene. However merit of paracetamol + dextropropoxyphene combination is controversial. Clinical trials have been inconclusive as to whether it has efficacy superior to either drug alone. Popularity of this formulation may be due to mild euphoric effect of dextropropoxyphene. The main disadvantage is that in cases of overdose death may occur within an hour due to the rapid absorption of dextropropoxyphene leading to respiratory depression.

3. Paracetamolcombinationwithcentralmusclerelaxants

Formulations containing paracetamol with four central muscle relaxants are available. Central muscle relaxants were previously indicated for spastic condition and are still prescribed but their use is declining owing to their doubtful value. These relaxants have not been included in the latest issue of Goodman and Gilmann's *Pharmacological Basis of Therapeutics* (1996 edition). If muscle relaxants are useful even then paracetamol does not provide any benefit if combined with these agents.

4. Formulationsofparacetamolwithantihistaminicsandnasaldecongestants

Various irrational formulations are available as cough and cold remedies containing antihistaminics, mucolytics, nasal decongestants and cough suppressants. These formulations are useless. In most such formulations paracetamol is one of the ingredients which is irrational.

5. Combinationofparacetamolwithvariousotherdrugs

(a) Dicyclomine: Dicyclomine is an antispasmodic useful for colicky pain. Combination of paracetamol does not produce any advantage but cost of the treatment is increased. Paracetamol is not useful in colicky pain.

(b) Orphenadrine: Orphenadrine is a drug for Parkinson's disease as it possesses potent central anticholinergic property. Additionally it is also a central muscle relaxant but this property is of doubtful utility. There is no justification of combining paracetamol with orphenadrine as paracetamol does not produce any beneficial effect in Parkinson's disease.

(c) Disodium hydrogen phosphate: Although only one preparation is available but without any benefit as disodium hydrogen phosphate is an alkalinizer. Here probably it is used as a diaphoretic (increases sweat) but paracetamol alone is useful if there is fever and in such cases it should be administered separately as and when required.

(d) Ergotamine: Paracetamol with ergotamine has some justification. Ergotamine is used for acute attack of migraine, addition of paracetamol products better effect as compared to ergotamine alone, so, this formulation is rational to some extent, but not necessary.

(e) Metoclopramide: This formulation is also rational to some extent due to the fact that metoclopramide increases the speed of absorption of paracetamol. Moreover, when this formulation is used for migraine attack, paracetamol provides some relief, and metoclopramide apart from increasing the absorption of paracetamol, corrects gastric disturbances in migraine (nausea, vomiting and slight degree of gastral paralysis).

In general, fixed dose formulations or combinations should not be prescribed unless there is good reason to consider that the patient needs all the drugs in the formulation and that the doses are appropriate and do not need to be adjusted separately ...

It can be concluded that paracetamol should preferably be prescribed separately whenever required as it provides symptomatic relief in mild to moderate somatic pain and in cases of fever, which is a symptom of various diseases, particularly infections. Paracetamol should not be used as a sleep(ing) companion.

Annexure6

Rofecoxib, Heart Attacks and the FDA: Testimony of David J. Graham, MD, MPH, November 18, 2004

Mr. Chairman and members of the Committee,

Introduction

Good morning. My name is David Graham, and I am pleased to come before you today to speak about Vioxx (rofecoxib), heart attacks and the FDA. By way of introduction, I graduated from the Johns Hopkins University School of Medicine, and trained in Internal Medicine at Yale and in adult Neurology at the University of Pennsylvania. After this, I completed a three-year fellowship in pharmacoepidemiology and a Masters in Public Health at Johns Hopkins, with a concentration in epidemiology and biostatistics. Over my 20 year career in the field, all of it at FDA, I have served in a variety of capacities. I am currently the Associate Director for Science and Medicine in FDA's Office of Drug Safety.

During my career, I believe I have made a real difference for the cause of patient safety. My research and efforts within FDA led to the withdrawal from the US market of Omniflox, an antibiotic that caused hemolytic anemia; Rezulin, a diabetes drug that caused acute liver failure; Fen-Phen and Redux, weight loss drugs that caused heart valve injury; and PPA (phenylpropanolamine), an over-the-counter decongestant and weight loss product that caused hemorrhagic stroke in young women. My research also led to the withdrawal from outpatient use of Trovan, an antibiotic that caused acute liver failure and death. I also contributed to the team effort that led to the withdrawal of Lotronex, a drug for irritable bowel syndrome that causes ischemic colitis; Baycol, a cholesterol-lowering drug that caused severe muscle injury, kidney failure and death; Seldane, an antihistamine that caused heart arrhythmias and death; and Propulsid, a drug for night-time heartburn that caused heart arrythmias and death. I have done extensive work concerning the issue of pregnancy exposure to Accutane, a drug that is used to treat acne but can cause birth defects in some children who are exposed in-utero if their mothers take the drug during the first trimester. During my career, I have recommended the market withdrawal of 12 drugs.

Only 2 of these remain on the market today-Accutane and Arava, a drug for the treatment of rheumatoid arthritis that I and a co-worker believe causes an unacceptably high risk of acute liver failure and death.

Vioxx and heart attacks. Let me begin by describing what we found in our study, what others have found, and what this means for the American people. Prior to approval of Vioxx, a study was performed by Merck named 090. This study found nearly a 7-fold increase in heart attack risk with low dose Vioxx. The labeling at approval said nothing about heart attack risks. In November 2000, another Merck clinical trial named VIGOR found a 5-fold increase in heart attack risk with high-dose Vioxx. The company said the drug was safe and that the comparison drug naproxen, was protective. In 2002, a large epidemiologic study reported a 2-fold increase in heart attack risk with high-dose Vioxx and another study reported that naproxen did not affect heart attack risk. About 18 months after the VIGOR results were published, FDA made a labeling change about heart attack risk with high-dose Vioxx, but did not place this in the "Warnings" section. Also, it did not ban the high-dose formulation and its use. I believe such a ban should have been implemented. Of note, FDA's label change had absolutely no effect on how often high-dose Vioxx was prescribed, so what good did it achieve?

In March of 2004, another epidemiologic study reported that both high-dose and low-dose Vioxx increased the risk of heart attacks compared to Vioxx's leading competitor, Celebrex. Our study, first reported in late August of this year found that Vioxx increased the risk of heart attack and sudden death by 3.7 fold for high-dose and 1.5 fold for low-dose, compared to Celebrex. A study report describing this work was put on the FDA website on election day. Among many things, this report estimated that nearly 28,000 excess cases of heart attack or sudden cardiac death were caused by Vioxx. I emphasize to the Committee that this is an extremely conservative estimate. FDA always claims that randomized clinical trials provide the best data. If you apply the risk-levels seen in the 2 Merck trials, VIGOR and APPROVe, you obtain a more realistic and likely range of estimates for the number of excess cases in the US. This estimate ranges from 88,000 to 139,000 Americans. Of these, 30-40% probably died. For the survivors, their lives were changed forever. It's important to note that this range does not depend at all on the data from our Kaiser-FDA study. Indeed, Dr. Eric Topol at the Cleveland Clinic recently estimated up to 160,000 cases of heart attacks and strokes due to Vioxx, in an article published in the New England Journal of Medicine. This article lays out clearly the public health significance of what we're talking about today.

So, how many people is 100,000? The attached Tables 1 and 2 show the estimated percentage of the population in your home State and in selected cities from your State that would have been affected had all 100,000 excess cases of heart attack and sudden cardiac death due to Vioxx occurred only in your State or city. This is to help you understand how many lives we're talking about. We're not just talking numbers. For example, if we were talking about Florida or Pennsylvania, 1% of the entire State population would have been affected. For Iowa, it would be 5%, for Maine, 10% and for Wyoming, 27%.

If we look at selected cities, I'm sorry to say, Senator Grassley, but 67% of the citizens of Des Moines would be affected, and what's worse, the entire population of every other city in the State of Iowa. But there is another way to put this range of excess cases into perspective. Imagine that instead of a serious side-effect of a widely used prescription drug, we were talking about jetliners. Please ignore the obvious difference in fatality rates between a heart attack and a plane crash, and focus on the larger analogy I'm trying to draw. If there were an average of 150 to 200 people on an aircraft, this range of 88,000 to 138,000 would be the rough equivalent of 500 to 900 aircraft dropping from the sky. This translates to 2-4 aircraft every week, week in and week out, for the past 5 years. If you were confronted by this situation, what would be your reaction, what would you want to know and what would you do about it?

Brief history of drug disasters in the US. Another way to fully comprehend the enormity of the Vioxx debacle is to look briefly at recent US and FDA history. The attached figure shows a graph depicting 3 historical time-points of importance to the development of drug safety in the US. In 1938, Congress enacted the Food, Drug and Cosmetic Act, basically creating the FDA, in response to an unfortunate incident in which about 100 children were killed by elixir of sulfanilamide, a medication that was formulated using anti-freeze. This Act required that animal toxicity testing be performed and safety information be submitted to FDA prior to approval of a drug. In 1962, Congress enacted the Kefauver- Harris Amendments to the FD&C Act, in response to the thalidomide disaster in Europe. Overseas, between 1957 and 1961, an estimated 5,000 to 10,000 children were born with thalidomide-related birth defects. These Amendments increased the requirements for toxicity testing and safety information preapproval, and added the requirement that "substantial evidence" of efficacy be submitted. Today, in 2004, you, we, are faced with what may be the single greatest drug safety catastrophe in the history of this country or the history of the world. We are talking about a catastrophe that I strongly believe could have, should have been largely or completely avoided. But it wasn't, and over 100,000 Americans have paid dearly for this failure. In my opinion, the FDA has let the American people down, and sadly, betrayed a public trust. I believe there are at least 3 broad categories of systemic problems that contributed to the Vioxx catastrophe and to a long line of other drug safety failures in the past 10 years. Briefly, these categories are 1) organizational/structural, 2) cultural, and 3) scientific. I will describe these in greater detail in a few moments.

My Vioxx experience at FDA. To begin, after publication of the VIGOR study in November 2000, I became concerned about the potential public health risk that might exist with Vioxx. VIGOR suggested that the risk of heart attack was increased 5-fold in patients who used the high-dose strength of this drug. Why was the Vioxx safety question important? 1) Vioxx would undoubtedly be used by millions of patients. That's a very large number to expose to a serious drug risk. 2) heart attack is a fairly common event, and 3) given the above, even a relatively small increase in heart attack risk due to Vioxx could mean that tens of thousands of Americans might be seriously harmed or killed by use of this drug. If these three factors were present, I knew that we would have all the ingredients necessary to guarantee a national disaster. The first two factors were established realities. It came down to the third factor, that is, what was the level of risk with Vioxx at low- and high-dose.

To get answers to this urgent issue, I worked with Kaiser Permanente in California to perform a large epidemiologic study. This study was carefully done and took nearly 3 years to complete. In early August of this year, we completed our main analyses and assembled a poster presentation describing some of our more important findings. We had planned to present these data at the International Conference on Pharmacoepidemiology, in Bordeaux, France. We concluded that high-dose Vioxx significantly increased the risk of heart attacks and sudden death and that the high doses of the drug should not be prescribed or used by patients. This conclusion triggered an explosive response from the Office of New Drugs, which approved Vioxx in the first place and was responsible for regulating it postmarketing. The response from senior management in my Office, the Office of Drug Safety, was equally stressful. I was pressured to change my conclusions and recommendations, and basically threatened that if I did not change them, I would not be permitted to present the paper at the conference. One Drug Safety manager recommended that I should be barred from presenting the poster at the meeting, and also noted that Merck needed to know our study results.

An email from the Director for the entire Office of New Drugs, was revealing. He suggested that since FDA

was "not contemplating" a warning against the use of high-dose Vioxx, my conclusions should be changed. CDER and the Office of New Drugs have repeatedly expressed the view that ODS should not reach any conclusions or make any recommendations that would contradict what the Office of New Drugs wants to do or is doing. Even more revealing, a mere 6 weeks before Merck pulled Vioxx from the market, CDER, OND and ODS management did not believe there was an outstanding safety concern with Vioxx. At the same time, 2-4 jumbo jetliners were dropping from the sky every week and no one else at FDA was concerned.

There were 2 other revelatory milestones. In mid-August, despite our study results showing an increased risk of heart attack with Vioxx, and despite the results of other studies published in the literature, FDA announced it had approved Vioxx for use in children with rheumatoid arthritis. Also, on September 22, at a meeting attended by the director of the reviewing office that approved Vioxx, the director and deputy director of the reviewing division within that office and senior managers from the Office of Drug Safety, no one thought there was a Vioxx safety issue to be dealt with. At this meeting, the reviewing office director asked why had I even thought to study Vioxx and heart attacks because FDA had made its labeling change and nothing more needed to be done. At this meeting a senior manager from ODS labeled our Vioxx study "a scientific rumor." Eight days later, Merck pulled Vioxx from the market, and jetliners stopped dropping from the sky.

Finally, we wrote a manuscript for publication in a peer-reviewed medical journal. Senior managers in the Office of Drug Safety have not granted clearance for its publication, even though it was accepted for publication in a very prestigious journal after rigorous peer review by that journal. Until it is cleared, our data and conclusions will not see the light of day in the scientific forum they deserve and have earned, and serious students of drug safety and drug regulation will be denied the opportunity to consider and openly debate the issues we raise in that paper.

Past experiences. My experience with Vioxx is typical of how CDER responds to serious drug safety issues in general. This is similar to what Dr. Mosholder went through earlier this year when he reached his conclusion that most SSRIs should not be used by children. I could bore you with a long list of prominent and not-so-prominent safety issues where CDER and its Office of New Drugs proved to be extremely resistant to full and open disclosure of safety information, especially when it called into question an existing regulatory position. In these situations, the new drug reviewing division that approved the drug in the first place and that regards it as its own child, typically proves to be the single greatest obstacle to effectively dealing with serious drug safety issues. The second greatest obstacle is often the senior management within the Office of Drug Safety, who either actively or tacitly go along with what the Office of New Drugs wants. Examples are numerous so I'll mention just a few. With Lotronex, even though there was strong evidence in the pre-approval clinical trials of a problem with ischemic colitis, OND approved it. When cases of severe constipation and ischemic colitis began pouring into FDA's MedWatch program, the reaction was one of denial. When CDER decided to bring Lotronex back on the market, ODS safety reviewers were instructed to help make this happen. Later, when CDER held an advisory committee meeting to get support for bringing Lotronex back on the market, the presentation on ways to manage its reintroduction was carefully shaped and controlled by OND. When it came to presenting the range of possible options for how Lotronex could be made available, the list of options was censored by OND. The day before the advisory meeting, I was told by the ODS reviewer who gave this presentation that the director of the reviewing office within OND that approved Lotronex in the first place came to her office and removed material from her talk. An OND manager was "managing" an ODS employee. When informed of this, ODS senior management ignored it. I guess they knew who was calling the shots.

Rezulin was a drug used to treat diabetes. It also caused acute liver failure, which was usually fatal unless a liver transplant was performed. The pre-approval clinical trials showed strong evidence of liver toxicity. The drug was withdrawn from the market in the United Kingdom in December 1997. With CDER and the Office of New Drugs, withdrawal didn't occur until March 2000. Between these dates, CDER relied on risk management strategies that were utterly ineffective and it persisted in relying on these strategies long after the evidence was clear that they didn't work. The continued marketing of Rezulin probably led to thousands of Americans being severely injured or killed by the drug. And note, there were many other safer diabetes drugs available. During this time, I understand that Rezulin's manufacturer continued to make about $2 million per day in sales.

The big picture. The problem you are confronting today is immense in scope. Vioxx is a terrible tragedy and a profound regulatory failure. I would argue that the FDA, as currently configured, is incapable of protecting America against another Vioxx. We are virtually defenseless. It is important that this Committee and the American people understand that what has happened with Vioxx is really a symptom of something far more dangerous to the safety of the American people. Simply put, FDA and its Center for Drug Evaluation and Research are broken. Now, I'm sure you have read the recent proposal to have the Institute of Medic ine perform a review of CDER and its drug safety program and make recommendations for fixing things up. Don't expect anything meaningful or effective from this exercise. Over the history of CDER's drug safety program, a number of similar reviews have been done. In the late 1970's, I believe that a blue ribbon panel recommended that there be an entirely separate drug safety operation in FDA with full regulatory authority. It wasn't implemented. During the 1980's and early 1990's, CDER organized its own "program reviews" of drug safety. The basic premise underlying each of these reviews was that the "problem" was with the drug safety group; it didn't fit into the Center. So, the charge given to the review panel members was always framed as "figure out what's wrong with drug safety, and tell us what to do to get it to fit in." There was and is an implicit expectation that the status quo will remain unaltered.

The organizational structure within CDER is entirely geared towards the review and approval of new drugs. When a CDER new drug reviewing division approves a new drug, it is also saying the drug is "safe and effective."When a serious safety issue arises post-marketing, their immediate reaction is almost always one of denial, rejection and heat. They approved the drug so there can't possibly be anything wrong with it. The same group that approved the drug is also responsible for taking regulatory action against it post-marketing. This is an inherent conflict of interest. At the same time, the Office of Drug Safety has no regulatory power and must first convince the new drug reviewing division that a problem exists before anything beneficial to the public can be done. Often, the new drug reviewing division is the single greatest obstacle to effectively protecting the public against drug safety risks. A close second in my opinion, is an ODS management that sees its mission as pleasing the Office of New Drugs.

The corporate culture within CDER is also a barrier to effectively protecting the American people from unnecessary harm due to prescription and OTC drugs. The culture is dominated by a world-view that believes only randomized clinical trials provide useful and actionable information and that postmarketing safety is an afterthought. This culture also views the pharmaceutical industry it is supposed to regulate as its client, over-values the benefits of the drugs it approves and seriously under-values,

disregards and disrespects drug safety.

Finally, the scientific standards CDER applies to drug safety guarantee that unsafe and deadly drugs will remain on the US market. When an OND reviewing division reviews a drug to decide whether to approve it, great reliance is placed on statistical tests. Usually, a drug is only approved if there is a 95% or greater probability that the drug actually works. From a safety perspective, this is also a very protective standard because it protects patients against drugs that don't work. The real problem is how CDER applies statistics to post-marketing safety. We see from the structural and cultural problems in CDER, that everything revolves around OND and the drug approval process.

When it comes to safety, the OND paradigm of 95% certainty prevails. Under this paradigm, a drug is safe until you can show with 95% or greater certainty that it is not safe. This is an incredibly high, almost insurmountable barrier to overcome. It's the equivalent of "beyond a shadow of a doubt." And here's an added kicker. In order to demonstrate a safety problem with 95% certainty, extremely large studies are often needed. And guess what. Those large studies can't be done.

There are 2 analogies I want to leave you with to illustrate the unreasonableness of CDER's standard of evidence as applied to safety, both pre- and post-approval. If the weather-man says there is an 80% chance of rain, most people would bring an umbrella. Using CDER's standard, you wouldn't bring an umbrella until there was a 95% or greater chance of rain. The second analogy is more graphic, but I think it brings home the point more clearly. Imagine for a moment that you have a pistol with a barrel having 100 chambers. Now, randomly place 95 bullets into those chambers. The gun represents a drug and the bullets represent a serious safety problem. Using CDER's standard, only when you have 95 bullets or more in the gun will you agree that the gun is loaded and a safety problem exists. Let's remove 5 bullets at random. We now have 90 bullets distributed across 100 chambers. Because there is only a 90% chance that a bullet will fire when I pull the trigger, CDER would conclude that the gun is not loaded and that the drug is safe.

Table 1. The percentage of each State's population age 18 years or older that would be affected if an estimated 100,000 excess cases of heart attack and sudden cardiac death due to Vioxx had all occurred in that State. The States are presented alphabetically. These are the States represented by members of the Senate Finance Committee.

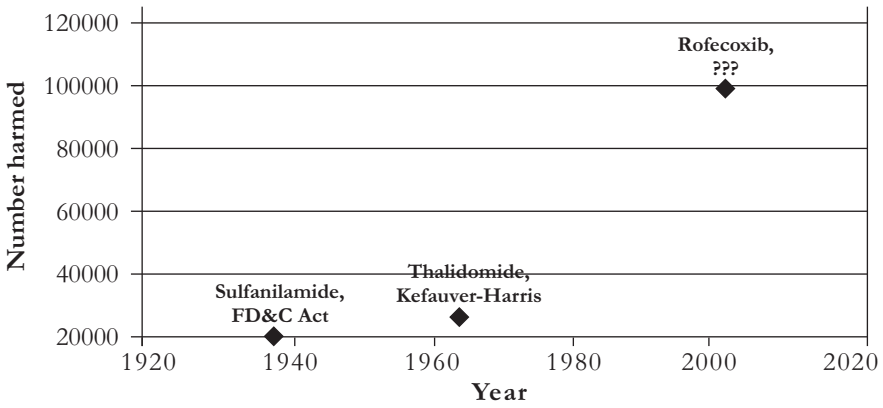
State	Estimated%ofpopulation age18yearsorolder
Arizona	2
Arkansas	5
Florida	1
Iowa	5
Kentucky	3
Louisiana	3
Maine	10
Massachusetts	2
Mississippi	5
Montana	14

State	Estimated%ofpopulation age18yearsorolder
New Mexico	7
North Dakota	21
Oklahoma	4
Oregon	4
Pennsylvania	1
South Dakota	18
Tennessee	2
Utah	6
Vermont	22
West Virginia	7
Wyoming	27

Table 2. The percentage of the population age 18 years or older from selected cities in the US that would be affected if an estimated 100,000 excess cases of heart attack and sudden cardiac death due to Vioxx had all occurred in that city. The cities chosen were from the more highly populated States shown in Table 1. These cities are in States represented by members of the Senate Finance Committee.

Stateandcity	Estimated%of population
Arkansas	73
Little Rock	
Arizona	66
Scottsdale	
Tuscon	27
Florida	
Orlando	72
Tallahassee	89
Tampa	44
Iowa	
Des Moines	67
All other cities	100
Kentucky	
Louisville	52

Stateandcity	Estimated%of population
Louisiana	
New Orleans	27
Oklahoma	
Oklahoma City	26
Oregon	
Portland	25
Pennsylvania	
Pittsburgh	40
Lancaster	100
Tennessee	
Nashville	23
Utah	
Salt Lake City	73



A brief history of drug safety disasters in the US

References

1. Census data for major US cities, 2000 census. Available at: URL: http://www.infoplease.com/ipa/A0108676.html. Accessed November 14, 2004.
2. Census data for states in the US, 2003. Available at URL: http://www.infoplease.com/ipa/A0004986.html. Accessed November 14, 2004.

Endnotes

[1] At <http://www.cochrane.org/>

[2] *Bulletin of Drug and Health Information (BODHI)*. Contact Dr P.K.Sarkar, Editor, email: <fha@cal.vsnl.net.in>.

[3] *"What is EBM?"* at <http://www.cebm.utoronto.ca/intro/whatis.htm>.

[4] Source: Sackett, D.L. et al. (1996) "Evidence based medicine: what it is and what it isn't." *BMJ* 312 (7023), 13 January, 71-72). This paper is also available on the Web at: <http://cebm.jr2.ox.ac.uk/ebmisisnt.html>

[5] Reproduced in public interest from website of Center for Evidence-Based Medicine, <http://www.cebm.utoronto.ca>

[6] Citations at <http://www.cebm.utoronto.ca/intro/>

[7] Citations at <http://www.cebm.utoronto.ca/intro/>

[8] Citations at <http://www.cebm.utoronto.ca/intro/>

[9] See *What is Evidence-based Medicine* and *What is Meta-Analysis* at <www.evidence-based-medicine.co.uk>

[10] See also "Evidence-based Medicine: where is the evidence and who should provide it*?", BODHI*, 50, Jan-Feb 2003, editorial.

[11] See in Chapter 5, "Forms of Entanglement".

[12] C M Gulhati. "Irrational fixed-dose drug combinations: a sordid story of profits before patients." *Indian J of Medical Ethics* at <http://www.issuesinmedicalethics.org/111ed005.html>.

[13] *Use of Essential Drugs: Model List (Eleventh List)*. World Health Organization, Geneva,1999.

[14] Beardshaw, V. *Prescription for Change*. Penang: IOCU/HAI, 1983. pp.19.

[15] Every issue of *MIMS India* gives a list of irrational combinations. For more wide-ranging lists, see also: Mira Shiva and Wishvas Rane. *Banned and Bannable Drugs*. VHAI, New Delhi, 2004.

[16] Phadke, Anant. *Drug Supply and Use: Towards a Rational Drug Policy in India*. Sage Publications, New Delhi, 1998.

[17] "Bangladesh Drug Policy - Criteria for recommended withdrawal of products from the Bangladesh market" in Zafrullah Chowdury's *The Politics of Essential Drugs* (1995), op.cit. Reproduced in Annexure 1 of Chapter 2.

[18] Patel Vikram , Vaidya R , Naik D , Borker P: "Irrational drug use in India: A prescription survey from Goa". *J.Postgraduate Medicine*. 51, Issue 1, 2005.

[19] Bangladesh Drug Policy, op cit.

[20] The list ofdrugs mentioned here is not exhaustive but only indicative. For a more complete list see *Banned and Bannable Drugs* (2004), op.cit.

[21] Sathyamala, C. *An Epidemiological Review of the Injectable Contraceptive, Depo-Provera*. MFC and Forum for Women's Health. Pune/Mumbai, 2000. Also see: Duggan, Lynn. "From Birth Control to Population Control: Depo-Provera in Southeast Asia" in McDonnell, Kathleen, ed. Adverse Effects: Women and the Pharmaceutical Industry. Penang: IOCU, 1986, pp.159-165.

[22] Worldwide sales of VIOXX in 2003 were $2.5 billion, making it a blockbuster for Merck.

[23] Rofecoxib belongs to the group of NSAIDs (nonsteroidal anti-inflammatory drugs) known as COX-2 selective inhibitors or coxibs (CycloOXygenase-2 InhiBitors). Being COX-2 selective means that these drugs act specifically on one form of the cyclooxygenase (COX) enzyme, namely the COX-2, whereas previous NSAIDs inhibited both COX-1 and COX-2. This specificity allows rofecoxib and other COX-2 inhibitors to reduce inflammation and pain while minimizing undesired gastrointestinal adverse effects - peptic ulcers - that are common with non-selective NSAIDs such as aspirin, naproxen, and ibuprofen.

It is currently unknown whether the increased risk of adverse cardiovascular events is common to all COX-2 inhibitors.

[24] See Chapter 5 for a brief discussion on clinical trials, randomization, etc.

[25] *Adenoma* refers to a collection of growths (-oma) of glandular origin. Adenomas can grow from many organs including the colon, adrenal, pituitary, thyroid, etc. These growths are benign, but some are known to have the potential, over time, to transform to malignancy (at which point they become known as adenocarcinoma.) A *polyp* is a smooth-coated abnormal growth (tumor) projecting from a mucous membrane. It is attached to the surface by a narrow elongated pedicle. Polyps are commonly found in the nose, urinary bladder, uterus, rectum, and large intestine. They may also occur elsewhere in the body where mucous membrane exists. In 2001, Merck commenced the APPROVe (Adenomatous Polyp PRevention On Vioxx) study, a three-year trial with the primary aim of evaluating the efficacy of rofecoxib for the prophylaxis of colorectal polyps.

Celecoxib had already been approved for this indication, and it was hoped to add this to the indications for rofecoxib as well. An additional aim of the study was to further evaluate the cardiovascular safety of rofecoxib.

The APPROVe study was terminated early when the preliminary data from the study showed an increased relative risk of adverse thrombotic cardiovascular events (including heart attack and stroke), beginning after 18 months of rofecoxib therapy. In patients taking rofecoxib, versus placebo, the relative risk of these events was 1.92 (rofecoxib 1.50 events vs placebo 0.78 events per 100 patient years). The results from the first 18 months of the APPROVe study did not show an increased relative risk of adverse cardiovascular events. (Bresalier *et al*., 2005). Previous Phase III clinical trials had also not shown this trend. (Swan, 2004)

In sum, the APPROVe study suggested that long-term use of rofecoxib resulted in nearly twice the risk of suffering a heart attack or stroke compared to patients receiving a placebo.

[26] "Conflicts of Interest on COX-2 Panel" at <http://www.cspinet.org/integrity/press/200502251.html>:
"The Food and Drug Administration on February 16-18, 2005 held an advisory committee meeting to discuss the cardiovascular risk posed by painkillers known as Cox-2 inhibitors, which include Celebrex, Bextra and Vioxx. The former two drugs are manufactured by Pfizer. The latter is manufactured by Merck. Novartis also has a Cox-2 inhibitor in its pipeline. At the end of the hearing, the FDA advisory panel voted to keep all three on the market, though with heightened warnings about the dangers posed by this class of drugs. At the request of the New York Times, the Center for Science in the Public Interest evaluated the 32 scientific experts chosen by the FDA to evaluate these drugs. The CSPI research uncovered affiliations between 10 of the scientists that served on the committee and the three manufacturers of Cox-2 inhibitors. This would appear to be a direct violation of the Federal Advisory Committee Act, which prohibits scientists with direct conflicts of interest from serving on panels offering advise to federal regulatory agencies. Another 17 scientists had other ties to drug manufacturers, though not the three with products under consideration at the meeting. According to a *New York Times* analysis of the votes, the advisory committee would have voted against Bextra and Vioxx staying on the market had scientists with conflicts of interest been excluded from the vote."

[27] Source: < http://gastroenterology.jwatch.org/cgi/content/full/2005/1230/11>

[28] For the testimony of Dr Graham before the Senate Finance Committee, see Annexure 6: "Rofecoxib, Heart Attacks and the FDA: Testimony of David J. Graham, MD, MPH, November 18, 2004". See also at the FDA website, <www.fda.gov/cder/drug/infopage/vioxx/vioxxgraham.pdf >, "Memorandum from David J. Graham, MD, MPH, Associate Director for Science, Office of Drug Safety to Paul Seligman, MD, MPH, Acting Director, Office of Drug Safety entitled, 'Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with COX-2 Selective and Non-Selective NSAIDs', September 30, 2004."

[29] See "Conflicts of Interest on COX-2 Panel" at <http://www.cspinet.org/integrity/press/200502251.html>, op.cit.

[30] As of Nov. 30, 2005, Merck reported that it has been served or is aware that it has been named as a defendant in approximately 9,200 lawsuits, which include approximately 18,250 plaintiff groups alleging personal injuries resulting from the use of the drug. In addition, as of Nov. 30, 2005, approximately 3,700 claimants had entered into Tolling Agreements with the Company, which halt the running of applicable statutes of limitations. And it is not just the United States victims that are suing the company. The Australian law firm, Slater and Gordon, has sued Merck in the Supreme Court of Victoria seeking damages for at least 400 victims, including family members of approximately 50 who died while taking the drug. Australian lawyers say that the number in Australia could reach into thousands.

[31] Source: *Journal Watch Gastroenterology,* December 30, 2005.

[32] Source: P A Francis: "Vicious Circle of Combinations", *Pharmabiz.com*. Reproduced with permission.

[33] 'Nimesulide: Drug linked to child deaths is still available in India'*BMJ* 2003; 326:70 (11 January)

[34] This part is from previously published by Anurag Bhargava in *Impoverishng the Poor*, op.cit.

[35] See also on page 127 of this most useful book, the commentary by Dr.P.K.Sarkar on Banning of Drugs.

[36] Source: *MIMS India*, Reproduced with thanks in public interest.

[37] Source: Central Drugs Standard Control Organization, Dte.Ghs, Ministry Of Health And Family Welfare, Government Of India, <http://www.cdsco.nic.in/>

[38] Reproduced in public interest from: Srivastava, Sachendra K. "Irrational Drug Combinations: Fixed Dose Paracetamol Combination with Various Drugs." *Bulletin of the Society for Rational Therapy*, Vol. 1, No. 4, July 1997.

Chapter 4
Marketing of Drugs

This branch of medicine had commonly been reckoned one of the most lucrative; for the subjects of it are generally found among the affluent: they are seldom without some complaint that requires assistance; and they measure their comforts too often by the quantity of medicine that is served up.

--*Trotter T.* A View of the Nervous Temperament Being a Practical Enquiry into the Increasing Prevalence, Prevention, and Treatment of Those Diseases Commonly Called Nervous, Biliary, Stomach and Liver Complaints; Indigestion; Low Spirits, Gout etc. *2nd ed. London: Longman, Hurst, Rees, and Orme, 1807: 231*

1. Pharma Scenario in India

India has a vast pharma market, and is rightly celebrated in international circles for making medicines very affordable and low-priced. As of 2003, the Indian industry was supplying 20 percent of the world's drugs (by volume) and is currently one of the largest pharma industries in the world (by volume). At least 60 manufacturing plants in India have US Federal Drug Administration (FDA) approval, second only to the United States. Currently a dozen top Indian companies are major suppliers to the US and European market as well as China.

In 2005, India's drug prices were among the lowest in the world (dollar terms and even in purchasing power parity terms) with China as the possible exception for even lower prices.

India's homegrown drug companies have outstripped Western MNCs *in India* (see Tables 1 and 2 and 3). But in comparison to worldwide pharma majors, the sales of entire Indian drug industry was US $ 10 billion (about Rs 40,000 cr) in 2005 whereas the sales of the top 15 companies in the world in 2004 was more than US $ 400 billion. In 2004, US drug companies spent more than US $ 33 billion in research whereas Western drug companies spent only US $ 33 million in India on R and D. Indian drug companies all put together spent US $ 0.3 billion on R and D. Just to give an idea of the disparity, merely world pharmaceutical packaging demand will reach US$ 22.20 billion in 2007. The US will remain the largest consumer of drug packaging while China generates the fastest gains.[1]

Nevertheless, the booming Indian pharma market coming to the rescue of generics world over, especially by making low priced antiretrovirals, is a good part of the story. The not so good part is that the Indian pharma scenario, as far as the ordinary poor consumer is concerned, is a failure of the market.[2]

As a result of this extreme market failure and failure of regulation in the absence of well-functioning markets, the drug (medicines) availability situation in India is one of poverty amidst adequacy - there is inadequate access and supply of even essential drugs to the poor despite adequate drug production. Adding to this misery is the poorly functioning public health system. While the sales of Indian Pharma

companies are increasing steadily (approximately Rs 40,000 cr during 2005, including exports), the total government expenditure by both Central and State Governments would be of the order of a mere Rs 3000 cr, with the Southern States spending 15 % on health of the total budget while Assam, Bihar, UP and Orissa would spend around 5 percent! Share of drugs to total treatment costs can vary from 50 to 80 percent depending on rural/urban locations and inpatient/out patient treatment. All-India figures for per capita annual drugs and other medical expenditure (rural) is Rs 294 out of Rs 380 for health as a whole.[3]

Table 1: Earnings by Top 25 Indian Pharma Companies

(Rs crore)	Net sales		Exports (FOB)		Imports (CIF)		Exports as % of sales	
	2004-05	2003-04	2004-05	2003-04	2004-05	2003-04	2004-05	2003-04
Ranbaxy Laboratories	3497.62	3398.27	2335.02	2346.07	716.64	531.03	66.8	69.0
CIPLA	2181.26	1842.24	1053.21	812.28	447.74	284.23	48.3	44.1
Dr Reddy's Laboratories	1557.69	1666.63	913.90	981.55	228.29	218.67	58.7	58.9
Aurobindo Pharma	1085.02	1259.89	554.62	642.04	530.69	539.58	51.1	51.0
Lupin	1161.13	1119.28	553.27	568.78	272.94	274.66	47.6	50.8
Orchid Chemicals & Pharma.	638.40	680.81	520.04	531.54	283.94	258.56	81.5	78.1
Ipca Laboratories	671.17	602.53	390.97	340.16	86.52	84.99	58.3	56.5
Biocon	646.51	502.51	376.15	299.98	281.63	211.17	58.2	59.7
Matrix Laboratories	636.76	529.48	336.60	297.59	160.05	98.37	52.9	56.2
Wockhardt	846.74	729.48	308.10	280.47	107.75	87.79	36.4	38.4
Divi's Laboratories	347.38	302.83	301.59	258.72	67.93	57.85	86.8	85.4
	995.62	839.36	275.10	204.11	108.01	91.67	27.6	24.3
Strides Arcolab	305.31	274.39	266.64	248.28	68.18	54.73	87.3	90.5
Panacea Biotec	325.54	261.62	227.74	161.55	148.06	112.84	70.0	61.7
J B Chemicals & Pharma	357.75	303.54	197.85	154.85	16.72	20.93	55.3	51.0
Cadila Healthcare	1063.40	1034.90	138.00	177.30	128.50	107.20	13.0	17.1
Glenmark Pharmaceuticals	463.20	320.02	130.13	48.95	43.70	29.67	28.1	15.3
Nicholas Piramal India	1232.25	1269.05	126.32	97.15	150.79	128.39	10.3	7.7
Alembic	524.46	556.46	105.91	124.29	80.68	71.09	20.2	22.3
Dishman Pharmaceuticals	157.22	123.25	105.88	83.42	40.63	26.05	67.3	67.7
Natco Pharma	154.40	129.61	91.85	61.67	11.12	9.64	59.5	47.6
Torrent Pharma	497.59	443.08	80.88	44.94	120.54	93.70	16.3	10.1
FDC	321.50	279.07	80.08	44.11	14.57	17.56	24.9	15.8
Unichem Laboratories	390.64	353.45	59.12	41.13	8.84	6.41	15.1	11.6
Medicamen Biotech	48.11	48.78	37.80	34.44	7.53	2.98	78.6	70.6
Total for 25 companies	20106.67	18870.53	9566.77	8885.37	4131.99	3419.76	47.6	47.1

Source: *Pharmabiz website*

Table 2: Highlights for Top 50 Indian Pharma Companies

	(Rs crore)		
	FY'05	**FY'04**	**% Change**
Net sales	29402.88	27380.32	7.4
Other income	1078.40	1047.28	3.0
Raw materials cost	14009.80	13190.92	6.2
Staff cost	2612.64	2216.37	17.9
Other expenditure	8069.18	7055.27	14.4
PBDIT	6438.54	6309.47	2.0
Interest	478.29	594.44	-19.5
Depreciation	1005.66	880.94	14.2
Profit before tax	4963.53	4836.38	2.6
Taxation	1028.48	804.68	27.8
Net profit after tax and exceptional items	4068.17	3878.22	4.9
Equity capital	1593.18	1434.62	11.1
NOTE:Totalsmaynotaddduetoroundingoff			

Source: *Pharmabiz website*

Table 3: World's Top 15 Pharma Companies Register 28% Growth in Net Profit, 10.6% Rise in Sales in 2004

(US$ Million)	**Sales**		**Cost of Mfg, Selling, R&D**		**EBDIT**		**Net Earnings**	
CompanyName	**2004**	**2003**	**2004**	**2003**	**2004**	**2003**	**2004**	**2003**
Abbott Laboratories	19680	17280	15782	14306	3898	2974	3236	2753
Amgen	9977	7868	6273	4836	4277	3520	3148	2539
AstraZeneca PLC	21426	18849	16971	14938	4455	3911	3813	3036
Bayer	40602	35872	39232	38731	1370	-2247	823	-1709
Bristol-Myers Squibb	19380	18653	14979	13720	4401	4933	2388	3106
Eli Lilly & Co	13858	12583	10591	9080	3267	3503	1810	2561
GlaxoSmithKline	39224	38133	27376	26557	11849	11576	8288	7964
Johnson & Johnson	47348	41862	34503	31909	12845	9953	8509	7197
Merck & Co	22939	22486	16316	14112	6623	8374	5813	6831
Novartis	28247	24864	21708	18975	6539	5889	5767	5016
Pfizer	52516	44736	38509	41490	14007	3246	11361	3910
Roche	27641	25143	22765	21170	4876	3973	5870	2472
Sanofi-Aventis	34680	30509	23543	21400	11138	9109	7159	5589
Schering-Plough	8272	8334	8488	7776	-216	558	-981	-92
Wyeth	17358	15851	13208	12152	4150	3699	1234	2051
Total for 15 Cos	403148	363023	310244	291152	93479	72971	68238	53224
Exchange Rate - As on 31/12/04: $ 1Euro = 1.36$ 1chf = 0.88$ As on 31/12/03 : $ 1Euro = 1.26$ 1chf = 0.81$								

Source: *Pharmabiz website*

More players in an uncontrolled market have meant only a wide range of prices for the same drugs. On the other hand, you have the same drug being sold by different companies (and sometimes by the same company) at vastly different prices. There is not even a direct relation between top-selling drugs and the real need, as per the disease and illness conditions prevalent. These severe distortions are compounded by poor regulation, nexus between medical profession and Pharma companies and their aggressive and often unethical marketing. We discuss these further in this chapter.

2. Marketing of Top 300 Drugs in India: A Brief Analysis

We now present an analysis of the top-selling 300 drugs of India accounting for Rs 19,000 crores sales in India.[4] This analysis of the Indian market is based on the October 2003 data of ORG-Nielsen. This data is collected from a sample of around 280 outlets in India and is based on data from *wholesale dealer's sales to retailers*. It is not based on retail sales. It is indicative of market trends in general. And in view of the sample taken and the exclusion of institutional sales, it is likely to be an underestimate of the total volume of sales.

This analysis of the top-selling brands, along with the analysis of the variation in drug retail prices already discussed gives us some insights into the nature of the Indian drug market.

The sales from 300 brands alone are huge and put the government estimates of the sales of the pharmaceutical sector into question. The government quotes lower figures. The Moving Annual Total from the retail sales of 300 brands alone (there are more than 20,000 formulations in the market) is a whopping Rs 18,000 crores. This figure of Rs.18,000 crores would only be a part of the total sales. The final figure of total sales does not take into account institutional and governmental purchases, which would also be of very considerable magnitude. Some industry estimates put the figure to Rs 40,000 crores (for instance see <www.pharmabiz.com> editorial, June 20, 2001: "A Rs. 40,000 crore industry"). It is interesting to note that the top 300 brands sell 50 percent of drugs by sales value (of Rs 18,000 cr) in India. This has to be seen in the context of sales of top-selling drugs in the world (see Table 4 and comment below)..

> *Global pharmaceutical sales tallied in at $500 billion. Of that revenue, $230 billion was in North America. That's more than double the dollar sales booked in the European Union. But cost differences become even more striking when one looks at the nine top-selling medicines in the world. Comparing the global sales figures released yesterday with the US sales figures released last month reveals that all but one of these medicines won most of its dollar sales in the United States. The reason is not likely merely that people in the US use more medicine, but also that they are more expensive.*[5]

Table 4: World's Top-Selling Drugs, 2003

Drug	Purpose	Maker	Global Sales ($bil)	US Sales ($bil)	% of Sales in US
Lipitor	Lowers cholesterol	Pfizer	$10.3	$6.8	66%
Zocor	Lowers cholesterol	Merck	6.1	4.4	72
Zyprexa	Anti-psychotic	Eli Lilly	4.8	3.2	66
Norvasc	Lowers blood pressure	Pfizer	4.5	2.2	40
Erypo (Procrit)	Treats anemia	Johnson & Johnson	4.0	3.3	83
Ogastro/Prevacid	Treats ulcers	Takeda & Abbott Laboratories)	4.0	4.0	100
Nexium	Treats ulcers	AstraZeneca	3.8	3.1	82
Plavix	Blood-thinner	Bristol-Myers Squibb	3.7	2.2	59
Seretide (Advair)	Treats asthma	GlaxoSmithKline	3.7	2.3	62
Zoloft	Anti-depressant	Pfizer	3.4	2.9	85

Source: *IMS Health, Forbes*

2.1 Top 300 Brands and their Relation to the National Essential Medicines List

There are a total of 354 drugs in the National List of Essential Medicines, which are adequate to take care of the majority of the health needs of the population during outpatient or inpatient care. If we examine the list of top 300 brands (as per ORG-Nielsen Oct 2003, see Table 5 for a partial list), we find that only 115 brands are of drugs that are mentioned in the National List of Essential Medicines (NLEM) 2003, i.e., only 38% of brands of the top selling ones are of drugs mentioned in the NLEM, the other 62% are of drugs which do not find mention in the NLEM. Of these 62% brands comprise drugs that are higher priced alternatives without a clear therapeutic advantage, and many drugs that are unnecessary, irrational and even hazardous. The number of drugs represented by these 115 brands is only 68.

That means the majority of the top selling brands are of drugs which are outside the National Essential Medicines List, which means that the majority of the drugs which are the most cost-effective for the treatment of priority health needs of the people are not the ones which are selling the most. (See also Table 6.)

A dramatic illustration of the lack of public health relevance of these top-selling preparations is the case of preparations for iron deficiency anemia, which is one of India's most prevalent public health problems. (See Table 7.)

There is not a single preparation in the top 300, which has the ingredients for an anemia preparation as mentioned in the National List of Essential Medicines.

The top selling preparation (Dexorange) is patently irrational (see Chapter 3) while others contain

substances which are not required (e.g., in Fefol-Z), and which can in fact impair iron absorption. (See also Table 7.)

Table 5: Top-Selling 25 Brands in India as per ORG-Nielsen Retail Audit, Oct 2003

	Brand Name	Uses and Remarks	Moving Annual Total in rupees crores
1	Corex	Cough suppressant. Abused as drug of addiction because of presence of codeine.	88.18
2	Becosules	Multivitamin, unnecessary preparation.	79.74
3	Taxim	Bacterial infections	77.05
4	Voveran	Pain relief	76.14
5	Althrocin	Bacterial infections	68.46
6	Human Mixtard	Diabetes mellitus	63.39
7	Cifran	Bacterial infections including typhoid	62.70
8	Liv-52	Ayurvedic liver preparation	62.67
9	Asthalin	Asthma.	61.76
10	Sporidex	Bacterial infections	61.71
11	Betnesol	Allergy	61.11
12	Zinetac	Dyspepsia, ulcer disease	60.70
13	Neurobion	Irrational Multivitamin preparation	60.27
14	Nise	Hazardous drug for pain relief	58.31
15	Digene	Antacid	57.86
16	Dexorange	Irrational preparation for anemia.	57.65
17	Phexin	Antibiotic for bacterial infection.	57.03
18	Mox	Bacterial infections	56.36
19	Cardace	Hypertension, heart failure, much cheaper alternatives exist	55.31
20	Rabipur	Vaccines against rabies	54.40
21	Omez	Peptic ulcer	53.52
22	Ciplox	Bacterial infections	51.69
23	Combiflam	Analgesic combination.	49.02
24	Aten	Hypertension	48.87
25.	Augmentin	Costly antibiotic	48.63
		Total	1532.53

The mere inclusion of a drug in the National List of Essential Medicines does not translate into affordability for the patient, because most of the drugs included in the NLEM, are outside price control. Even when the drug is under National List of Essential Medicines because of the lack of regulation over drug prices, it is often the costlier version that sells more: For example, Ciprofloxacin is sold by Ranbaxy at Rs.8.96 a tablet. Yet the cheapest brand of Ciprofloxacin at Rs.2.90 does not sell as much.

Table 6: Top Selling 10 Categories of Drugs in the Top 300 Brands: Where is the People's Money Going?

Type of drug category	No. of Brands	Moving annual total (in crores of rupees)	Remarks
1. Anti-infectives	65	1650.02	Most frequently used and abused drugs when antibiotics are given for fever due to viral infections
2. Analgesics	26	705.06	Hazardous analgesics like nimesulide are one of the top sellers.
3. Endocrine disorders like diabetes mellitus, hormones	25	694.10	
4. Multivitamins and minerals	27	651.29	Contains predominantly non-essential drugs in all kinds of irrational combinations.
5. Drugs for cardiovascular disease	26	601.64	The top selling cardiovascular drug is one that has little therapeutic advantage over less costly alternatives.
6. Drugs for respiratory system, including cough preparations	21	512.59	Cough syrups sell more than drugs for asthma.
7. Drugs for gastrointestinal system	20	427.21	Their large sale is also the result of over prescription.
8. Drugs for allergy	10	326.51	
9. Anticonvulsants	9	221.35	
10. Hematinics	6	128.13	Contains such irrational wonders of the pharmaceutical world as Dexorange (57 crores) which till recently contained animal blood from slaughter houses, hepatoglobine, etc.

2.2 Top-Selling Drugs Outside the NLEM

These are of diverse types and include:

- Higher priced brand of either the same drug or a higher priced alternative to a lower cost essential drug.
- Irrational drugs and irrational combinations of antibiotics, vitamins, analgesics which include unsafe and hazardous drugs.

Examples abound in this regard:

- Cifran brand of ciprofloxacin is the largest selling antibiotic, whereas it is the costliest among the

ciprofloxacins. Other brands of ciprofloxacin (e.g., Zoxan) although three times cheaper, sell five times lesser than Cifran.

- Ramipril is an angiotensin converting enzyme inhibitor like enalapril. It has no therapeutic advantage over enalapril, and is costlier. Enalapril is mentioned in both the National and the WHO list of essential medicines as being representative of the class of ACE inhibitors, while ramipril has not been mentioned. Yet ramipril sells more than enalapril.

- Penicillins including amoxycillin, ampicillin are effective antibiotics for a variety of infections. Oral cephalosporins are to be used in certain situations only, and mainly when it is not possible to administer oral penicillins because of penicillin allergy. Yet according to the sales figures, brands of cephalosporins (Phexin, Sporidex) clearly outperform penicillins, which indicates inappropriate use. The indications for erythromycin are similarly limited. However the sales figure for erythromycin is higher than that of penicillins.

Irrational combinations of drugs, which only add cost but no therapeutic value, are touted as effective remedies and promoted aggressively. This is another area of concern.

Table 7: Most Common and Important Public Health Problem of India According to the Pharmaceutical Industry: Not Anemia, but B-Complex Deficiency!

Brand	Rank in Top 300 Brands	Moving Annual Total (rupees crores)
Becosules	2	79.74
Revital	27	47.64
Polybion	42	40.85
Zincovit	60	32.26
Cobadex forte	88	26.10
Methycobal	116	21.87
Zincovit	118	21.65
Neogadine	119	21.52
Riconia	125	20.78
R.B. Tone	129	20.21
A to Z	145	19.07
M2tone	157	18.22
Supradyn	221	15.25
Becadexamin	229	14.63
Raricap	239	13.89
Becosules-Z	295	12.03
Optineuron	297	11.97
Total		437.68

2.3 Irrational Drugs of No Therapeutic Value in the Top 300

Consider the following:

- Irrational drugs like Electral (since rationalised), or drugs which are used irrationally like Evion, Glucon-D, Deca-durabolin are top selling drugs. Protein products are irrationally prescribed and irrationally priced.

- Irrational combinations of vitamins, minerals, and other ingredients including ginseng (which has supposedly aphrodisiac properties), or even an outmoded and dangerous ingredient like animal hemoglobin from slaughterhouse blood, fresh liver extract, are passed off as tonics, haematinics, and food supplements to a gullible population via the medium of obliging doctors. Most of these preparations would be hard to find in any pharmacopoeia in the world, but the drug regulatory authorities do not find anything wrong in approving their manufacture. Examples include Revital, elixir Neogadine, hepatoglobins, etc. (See also the box *Banning of Liver Extract* below and the box on Dexorange in Chapter 3, Section 5.5.)

- Irrational combinations of antibiotics: the commonest being ampicillin plus cloxacillin which is widely and inappropriately used.

2.4 Unsafe and Hazardous Drugs Among the Top 300

- Preparations containing animal tissue without therapeutic rationale, e.g., Hepatoglobin containing fresh liver extract carry the risk of transmitting infection.

- The high sales figures for codeine containing cough syrups are a matter for concern. Both Corex (the Number 1 brand in the country with sales of Rs 88 crores) and Phensedyl (rank 29, sales Rs 47.30 crores) are syrups widely used especially in the Northeast as drugs of addiction because of the presence of codeine. They are also smuggled into neighbouring countries like Bangladesh and Myanmar. Does the abuse of these syrups contribute to their high turnover? In contrast Glycodin contains dextromethorphan which is a safe constituent. It however does not sell as much (rank 259, sales Rs 13.15 crores).

- Nimesulide, which is one of the best-selling analgesic drugs in India, is not approved in most of the developed world because of its side-effects on the liver.

2.5 Preponderance of Combinations Among the Top 300

- A significant number of the top selling formulations are combinations of drugs, rather than single ingredients. In fact, there are 118 combinations in the list of 300. The majority of the combinations are irrational. Only around 20 of these combinations are rational, the rest are combinations that lack any therapeutic rationale for being combined.

- The pattern of production and the pattern of sales do not adequately reflect the real health needs of the people. There is over-representation of costly antibiotics, irrational multivitamin preparations,

cough syrups, ineffective haematinics, pain balms, rather than cost-effective drugs of real therapeutic value.

- The sales figures reflect the fact that in India, drugs which are not considered essential sell more than rational and essential drugs, that costlier drugs most often sell more than cheaper alternatives (even those made by well known manufacturers), and downright irrational and hazardous drugs are among the top-sellers. The majority of sales are coming from the sales of drugs not considered relevant by experts for inclusion into an essential medicines list, and not considered important by the government for regulation of their price.

Banning of Liver Extract

P A Francis

A large number of pharmaceutical products with poor rationality profiles are being manufactured and marketed by drug companies in India today. Most of them are fixed dose combinations of drugs and vitamin preparations. No control on their growth has been achieved despite frequent regulatory interventions. One such controversial preparation are brands containing crude animal liver extracts with a few other ingredients for the treatment of megaloblastic anemia. These formulations have been found to be carrying infective diseases from animals to humans besides causing allergic reactions as they are containing biological products. Currently there are six leading brands of liver extract formulations available in the market for the treatment of anemia. These are Livogen, Ibberol, Plastules B12, RB Tone, Heptaglobine and Hep-Forte. Recent medical studies conducted in India and abroad have questioned the relevance of the continuing use of anti-anemic preparations containing multiple ingredients like liver, iron, folic acid, vitamin B 12, copper, manganese, etc. Some of these ingredients are unnecessary, wasteful and only increase the cost of therapy and risk of infection, the studies have pointed out. But none of the pharma companies had taken any steps to withdraw the liver extract from their products or reformulate them although the use of liver extract has been banned in several countries long ago

The need to ban the use of liver extracts in drug preparation was first raised by Pharmabiz.com in April 2001. The issue was subsequently taken up by Ahmedabad-based Consumer Education Research Centre with DCGI. But no serious action was initiated by the Drug Controller General of India in this regard. DCGI is reported to be now moving to prohibit the use of liver extracts. A circular is expected to be issued in this regard asking the pharma companies to replace liver extract with pure Vitamin B12. Merck, the leading player in this segment, meanwhile, has decided to withdraw liver extract from its brand, Livogen. Liver extract has been the key ingredient of Livogen tablet and the tonic marketed by the company. The decision of the company is in the wake of its acceptance of the fact that this ingredient has no place in modern therapy as it is unsafe and irrational. Liver extracts used to be the only option before the development of folic acid and vitamin B12 in pure form. But the drug companies have been avoiding use of Vitamin B12 in place of liver extracts despite its abundant availability. Reluctance of the drug companies is mainly on account of the cost factor. Regulatory authorities should know that resistance of pharma companies to recall an established product or change the composition of a well known brand do cause a lot of damage to the public. In matters like this, a faster regulatory initiative is called for.

Source*: Pharmabiz*, June 19, 2002[6]

This brief analysis[7] of the top 300 brands suggests that the Indian doctors are prescribing drugs without adequate concern for evidence of their efficacy, safety, and cost. This is because of poor access to unbiased information on drugs, for doctors as well as lay persons in India, compounded by the aggressive and often misleading drug promotion by the drug industry. The result is increased health care costs for the patients, irrational use of drugs, and exposure of patients to the risks of unsafe drugs.

3. Marketing of Drugs and the Abandoning of Quality and Ethics

Drug companies in India and abroad have been notoriously lax in ethical consciousness although many of them talk of quality concerns. Human rights, including rights of workers manufacturing the drugs and people consuming them, are not a major issue with drug companies. Consider the following incidents involving drug companies and regulatory authorities that involve bypassing of quality and ethical norms:[8]

3.1 Boehringer-Mannheim and Cotrimoxazole

"The FDA in Maharashtra ordered a nation-wide recall of the antibacterial drug Comsat Forte, a brand of cotrimoxazole, of Boehringer-Mannheim, (India) Limited when it was found to contain the antidiabetic ingredient glibenclamide as a result of mix-up in raw materials on the shop floor of the manufacturing plant. Rather than cure infections, the tablets caused a drastic fall in blood sugar and blood pressure, and 62 people turned critical after using it at an eye camp in Ahmednagar on August 16, 1996. Although the deadline for recall expired on September 5, the drug claimed two lives in Kolar, Karnataka, and five days later, the company's Managing Director left India for Canada. The Maharashtra FDA has been reported to have opined that the multinational company is over 125 years old and that its reputation had to be considered before taking any precipitate action. Is this ethical?" [9]

3.2 Letrozole Affair

Over 400 women were allegedly used as "guinea pigs" by some researchers to test the anti-cancer drug, Letrozole, for curing infertility through induction of ovulation. The clinical trials allegedly took place without the permission of the Drug Controller General of India at private clinics in places like Delhi, Nagpur, Hyderabad, Kolkata and Jodhpur. Letrozole belongs to Schedule G of the Drugs and Cosmetics Rules and can be sold only against prescriptions from cancer specialists. Based on documents submitted by the innovator of the drug, Novartis, US Food and Drug Administration and British Medicines and Healthcare Products Regulatory Authority have labeled it as embryotoxic and fetotoxic at miniscule doses. [See news report "Doctors in India prescribe unapproved fertility drug" in the *British Medical Journal*, BMJ 2003; 327:768 (4 October)]

3.3 The Case of Nimesulide

We have already discussed the way nimesulide continues to be marketed in India despite adverse reports everywhere. (See Chapter 3 on *Rationality of Drugs*)

3.4 Justice Lentin's Observations

Nearly 20 years ago Justice Lentin had documented a criminal nexus between officials of Maharashtra FDA, drug industry and certified quality labs.

In its foreword to the report, the Lentin Commission said: " These pages describe and illustrate the ugly

facets of the human mind and human nature, projecting errors of judgment, misuse of ministerial power and authority, apathy towards human life, corruption, nexus and quid pro quo between unscrupulous license holders, analytical laboratories, elements in the industries department controlling the award of rate contracts, manufacturers, traders, merchants, suppliers, the Food and Drugs Administration and persons holding ministerial rank."

(See Annexure 1, *Landmark Incidents in Unethical Marketing of Drugs* for more details.)

3.5 Glaxo Sells Expired Drugs - the Glaxo Scandal

Even leading drug manufacturers like Glaxo have been incriminated in this regard, when they were found to be selling expired drugs to a scrap dealer instead of destroying them. We know of no other country in the world where an extreme step like consideration of a death penalty has been proposed as a deterrent to the problem.

The Maharashtra State Food and Drug Administration (FDA) ordered the closure of the production of the British multinational company, Glaxo (India), at its Worli factory in Bombay, for 10 days in March 1994, for violating the provisions of the Drugs and Cosmetics Act and the rules of FDA. In June 1993, the FDA found that Glaxo, instead of destroying rejected drugs had authorised a scrap dealer to collect the substandard drugs from its premises. These drugs were then recycled and sold in black market, putting unwary consumers to grave risk.

The FDA seized large stocks of unlabeled drugs like Betnesol, Viteneuron and Repalin Forte injections manufactured by Glaxo, rubber stamps and also large stocks of coded and plain Glaxo labels from the scrap dealer's godown in Dharavi slum area. Following the discovery of labelled and unlabeled drugs, coded and blank labels, and printed cartons in the factory's unit in the presence of the company's quality assurance manager and the general manager, the company was issued a show-cause notice. On June 14, 1993, FDA suspended Glaxo's licence to manufacture various drugs for ten days from July 15 to 24, 1993. However, Glaxo appealed to the State Health Minister against this order.

3.6 Selling of Substandard TB Drugs by Reputed Companies

We quote from the *Indian Express* of Aug 4, 2003:[10]

> **RANCHI, AUGUST 3:** The Jharkhand Drug Administration has imposed a state-wide ban on the use and distribution of five medicines manufactured by Lupin Ltd, Aurangabad, Nestor Pharmaceuticals Ltd, Faridabad and Pure Pharmaceuticals Ltd.
>
> These medicines, Pyrazinamide IP-750mg, Isoniazid (Tab) IP-300mg, Pyridoxinc IP-5mg, Ethambutol (Tab) IP-600mg and Rifampicin (Cap), are prescribed to TB patients and were supplied to hundreds of government-run hospitals in the state by the Union Health Ministry last year.
>
> State Drug Controller Vinay Mohan Prasad said: "Samples were collected by drug inspectors from Ranchi, Hazaribagh, Dumka and Dhanbad. Laboratory test confirmed the suspicion that these

medicines were of substandard variety."

In his July 28 letter circulated to all civil surgeons, superintendents of state-run hospitals in 22 districts of the state and Jharkhand Chemists and Druggists' Association (JDCA) Prasad has stated that "the ban is being imposed on use and distribution of the above medicines".

Person incharge of SL, Dr. B.N. Sinha, in his March 23 report to Prasad states: "In the opinion of the undersigned, the samples selected 'do not conform' to the claims in respect of the test performed". Explaining Sinha's report, Prasad said: "This means these medicines lack potency as per the claims made by the manufacturers."

3.7 Diethylene Glycol Poisoning Revisited

The specific incident of diethylene glycol poisoning in Gurgaon is shocking for its lack of care. The evidence in the episode pointed to a common drug exposure. But the district and state drug controller gave the suspected batch of drugs a clean chit. Yet the doctors persisted …

> ... the district and the state drug controller had tested many samples using thin layer chromatography before a sample of medicine tested positive for diethylene glycol at the Central Drug Testing Laboratory, Calcutta …. This indicates that thin layer chromatography alone may not identify contamination with diethylene glycol. On the other hand gas liquid chromatography or other appropriate methods are not available in all the laboratories that may be asked to test medicines. The failure to detect the contamination using thin layer chromatography had an important bearing on these cases. Once contamination was suspected and the samples were sent for testing, the number of cases suddenly declined. After the samples were declared not to be contaminated, 6 more cases occurred. Further cases were only stopped because scientists suspected contamination and insisted that the suspect medicines should not be used unless found to be uncontaminated using gas-liquid chromatography ...

This clearly illustrates that the district and state drug controller could not detect the lethal contamination of the drug with diethylene glycol and it was only the Central Drug Testing laboratory at Kolkata that could detect it. Is this not a serious matter in a case where more than 30 innocent children died because of the greed and unscrupulousness of a drug manufacturer and the lax regulatory framework in the country?[11]

More recently, the entire TB drug consignment of rifampicin capsules exported by a leading anti-TB drugs manufacturer was returned by the authorities in south Africa after detection of poor blood levels with the drugs.

We discuss below, and elsewhere in the book, instances where regulatory agencies like the Drug Controller's office have capitulated to the demands of the drug companies, or acquiesced in illegal and unethical trials - acquiesced knowingly, or not taking action, or by ignoring violations of ethics: in effect leading to "regulatory capture" by drug companies and research groups/CROs (Contract Research Organisations).

3.8 Case of Zinc, etc., in Haematinic Preparations[12]

On the recommendations made by the Drug Technical Advisory Board (DTAB), the Drug Controller General of India (DCGI) had directed the state drug authorities in 1999 not to allow the manufacture of iron preparations containing zinc, amino acids and vitamins other than folic acid and vitamin C from August 31, 2000. Zinc, among other things, is known to interfere with the absorption of iron; excess zinc in pregnant women is known to increase premature delivery and stillbirth.[13] The DCGI directive had further stated that haemostatic preparations containing ferrous or ferric salts should provide elemental iron between 25 mg to 30 mg prophylactic use and between 60 mg to 100 mg therapeutic daily use. The DTAB, with probably some of the best brains from amongst pharmaceutical and medical sciences in this country, is considered to be the supreme authority in the country to advise the office of DCGI. Yet, the DCGI informed the state drug controllers after almost one year that the whole matter is being referred to the expert committee of DTAB and recommendations of this committee would be examined by DTAB for taking a *final* view in this matter. Until then, the instructions issued by DCGI in respect of iron preparations were to be kept in abeyance. The change of mind of the DCGI was music to 300-odd drug companies, including Franco-Indian, Raptakos-Brett, Parke-Davis, etc., which were, and are, making these preparations at huge profits for several years. There are also other majors in this business. These companies had built their brands over the years and a sudden halt of the sales of these products would definitely hit their bottomlines. It does not take a whole lot to guess what must have happened behind the scenes.

Quality and ethics is not a prerogative, if at all, of big companies and in fact there is no straightforward correlation observed between the size of a drug company and its quality and ethics consciousness.

CBI case against Johnson & Johnson

(*The Tribune*, Jan 25, 2002)

New Delhi, January 24

The CBI has registered a case against two Mumbai-based firms, including multinational Johnson and Johnson Ltd, for allegedly causing Rs 50 crore losses to the government besides cheating consumers by overpricing drugs.

Johnson and Johnson was found to be allegedly availing of exemption from price approval provided to small scale drug units by "fraudulently" floating a small scale unit N.R. Jet Enterprises and showing that such drugs and medicines were not manufactured by it, a CBI press note here said.

During investigations, the agency found that Jet Enterprises was controlled by employees of Johnson and Johnson and some of the products being manufactured by it were earlier being produced by the multinational, the release said , and adding that these medicines were still being promoted as products of Johnson and Johnson.

The CBI alleges that one such medicine, Raricap, was earlier marketed by Johnson at a retail price of Rs 16.24 per 40 tablets as fixed by the government under the provisions of the Drug Price Control Order 1995. However, the said product is being now manufactured by Jet Enterprises and is being sold at a retail cost of Rs 55.

Johnson and Johnson officials were not immediately available for comments.

4. Manipulating Quality

What does quality of drugs mean to the consumer? How is bad quality promoted?

4.1 Parameters of Quality

A drug should act for what it is prescribed for. Thus aspirin bought for say relief from headache should actually do so. We assume that the diagnosis of the doctor is correct. When one stores the drug in a cool, dark place, as many medicines are supposed to be, it should still be effective when one has a headache the next time around. The aspirin should not disintegrate, as it is wont to, if it is not made properly. Aspirin absorbs water (is hygroscopic) and can turn into powder if not stored properly.

All drugs have a declared shelf life between 18 months to 5 years. A consumer has a right to expect that a well-manufactured drug is effective for the period of its shelf life.

Also during this period, when it says 500 mg on the label, it should continue to have 500 mg or near that amount during its shelf life. Also, the drug should easily dissolve in the blood stream (within 15 minutes for an uncoated tablet, and within 60 minutes for a coated tablet); should not be too hard or too brittle; should not develop fungus or any kind of spots; or get chipped (become friable) at the edges or get broken by normal handling.

Similarly a syrup, IV fluid or injection, should not have any foreign particles floating in it or develop fungus or any other chemical reaction with its other constituents or with its container.

A manufacturer ensures quality by taking several steps to ensure quality as perceived by the consumer. In addition, manufacturers are expected to test for several chemical, physical, biological and other parameters including factors like appearance or smell. Acceptable standards are prescribed for all these in Indian Pharmacopoeia (IP) or British Pharmacopoeia (BP) or USP or pharmacopoeias of Europe, the WHO, etc. A drug manufactured as per IP is expected to follow standards prescribed in IP. These standards are checked for each and every raw material and excipients like binding agents that go into the making of a drug. Additionally tests are carried out for disintegration, weight variation, friability, hardness, etc. during the process of manufacture, say every 15 minutes, and finally from a suitable sample of the entire batch after manufacture.

In addition to ensure that the drug 'behaves' during its life time there are ways of measuring and predicting stability of the drug. And most obviously, as a part of post-marketing drug surveillance, samples need to be picked from the market and tested for quality.

Unacceptable quality of a drug, and therefore liable to be rejected by manufacturers, is when any one of the say 25 parameters that define the quality of a drug - its principal constituent and its excipients included - does not meet within the accepted standards as specified in the respective pharmacopoeia. Quality of a drug is also defined by the mode of packaging and the material used (glossy and attractive packaging is not always good quality).

In addition a whole set of practices called Good Manufacturing Practices (GMP), are recommended for

putting into practice, that ensures quality of drugs. GMP is largely common sense, cleanliness and hygiene and some systematic documentation to ensure the same. From July 2005, a new set of standards, called Schedule M, is required by drug control authorities in India.

Quality comes with an attached cost. However it is not very costly to be quality conscious. Quality in the final analysis, like evidence-based medicine or honesty, is an attitude of mind.

Recently, there have been attempts internationally to harmonise quality and regulatory standards. These attempts are good in the sense that countries, especially their regulatory agencies, are forced to up the standard bar so as to meet internationally accepted (read EU and US) standards. But sometimes this may result in increase in mere paper work, or a country's companies and/or regulatory agency may not be ready for the transition, especially if it is not properly sequenced and is done overnight. In the case of India, some of the new standards need to be scientifically questioned (say for instance Schedule M requirements) especially when quality is interpreted as more technology investments in a manufacturing facility without real perceptible changes in quality of production, regulation and ethical consciousness. As has been pointed out in the context of harmonisation:[14]

- applying ICH (International Conference on Harmonisation) standards and processes to non-ICH countries will increase costs and hamper access to necessary medicines, particularly interchangeable multi-source medicines (IMMs);
- WHO is the more appropriate intergovernmental organisation to set international standards; and
- regional efforts are difficult to arrange and may result in the domination of the area by the strongest regulator involved.

Often such hasty harmonisation can act as self-imposed trade barriers. Something, which is to be watched out for when a country "offers", say, health services and related sectors, under GATS (General Agreement on Trade and Services).

4.2 How is Bad Quality Promoted?

There are a variety of ways that substandard, subtherapeutic and spurious drugs get promoted in the market. These are some of the ways and consumers need to watch out:

1) By ignoring basic manufacturing requirements as indicated above, that is negligence, poor ethics and a "chalta hai" (will-do) attitude.

2) By making drugs at the lower end of the tolerance limit allowed: A 500 mg paracetamol tablet would be passed in quality control if it has the active ingredient between 450 to 550 mg (plus/minus 10%). During its shelf life, the 450 mg tablet's potency may decrease and may not act as desired.

3) By inappropriate packing: for instance, water-absorbing drugs like aspirin and ethambutol should be protected from high humidity during manufacture and storage during the entire life of the drug.

4) By committing criminal acts like putting haldi powder (turmeric) for tetracycline or sugar pill for calcium lactate: they harm the patients by not acting at the time of need. Again careless manufacture, especially in the case of IV fluids and injections, have been known to kill.

5) By consciously putting unnecessary products in the market and claiming undue benefits for them. (This can happen with essential drugs also when companies claim benefits not warranted by scientific research.) Some addictive substances like alcohol may be added in tonics, and the tonic as a whole is then claimed to be a stimulant. Or promoting substances that are sedatives but have the side-effect of increasing appetite; the drug is then marketed as an appetite stimulant.

6) By trying to bribe drug and other officials, and succeeding in evading compliance of desirable manufacturing practices. Also trying to bribe/induce doctors to prescribe one's own products, by influencing medical college departments for favourable research reports, by denying the efficacy of cheaper and safer alternatives, bad quality is ultimately promoted in the system. Everybody loses in the process.

7) By trying to come into the market for short-term purposes only: say, merely to fulfill an export order or a government order of, say, Rs. 10 crores. This can be done by loan licence manufacture and then disappearing (the so-called fly-by-night syndrome). Every manufacturer has an obligation to disclose sources and uses of funds, balance sheets, details about promoters and who is behind the company. In short, manufacturers need to be accountable to the public.

5. Prevalence of Spurious Drugs

The Indian media, especially during 2003 and after, started talking, almost in a chorus, of spurious drugs and estimates were bandied as to the extent of spurious drugs. The Government-appointed Mashelkar Committee (2002-03) examined various estimates, widely varying, and, often fueled on guesstimates and speculation, and concluded that there is no authentic data on the extent of the problem. "Based on the samples tested by the State authorities, data were analysed for the period 1995-2003. According to these data, the extent of sub-standard drugs varied from 8.19 to 10.64% and of spurious drugs varied between 0.24 % to 0.47%." (See box *What is a Spurious Drug?)*

5.1 Factors Contributing to Spurious Drugs

Several possible factors contribute to proliferation of spurious drugs. Some of the prominent ones pointed out by the Committee are:

a. Lack of enforcement of existing laws
b. Weak penal action
c. Very remunerative trade
d. Large scale sickness in small-scale pharmaceutical industry
e. Availability of improved printing technology that helps in counterfeiting
f. Lack of coordination between various agencies
g. Too many retail and wholesale chemist outlets
h. Inadequate cooperation between stakeholders.
i. Lack of control by importing/exporting countries
j. Widespread corruption and conflict of interests (See boxes below, *What's the Actual Situation on the Ground* and *Paucity of Testing Laboratories)*

First, adulterated food. Next, an adulterated cement construction collapsed on his head! Next a case of adulterated medicine. After that ...

R. K. Laxman in *The Times of India*

The Mashelkar Committee recommended total overhauling of the drug control administration and a structure, almost like that of the US FDA, involving several divisions as also a centralised regulator called the Central Drug Administration (CDA). This is a radical departure from the existing structure, which is a decentralised one as health and pharmaceuticals come under the concurrent list of the Constitution - to be looked after by both the Center and the States. The move, obviously to break the nexus between drug companies and State FDA officials, runs the risk of over-centralizing in a vast country like India. The Committee however has lost a good opportunity to recommend putting pricing policy and health related drug policy under the ambit of one single authority.

The Mashelkar Committee had toned down its earlier recommendations for death penalty to make offences of spurious drugs manufacturers "cognisable and non-bailable". The Government of India has nevertheless gone ahead and introduced a bill in the Parliament awarding capital punishment to those indulging in manufacture or sale of spurious drugs in the Parliament. One suspects that this was at the behest of the big manufacturers who are worried at the many me-too copies, genuine and fake. However the Committee has not addressed the problem of unlimited profiteering and the presence of irrational and

What is a Spurious Drug?

The definition of spurious drug was included in the Drugs and Cosmetics Act by the Amendment Act of 1982. Section 17-B defines that a drug shall be deemed to be spurious:

a) if it is manufactured under a name which belongs to another drug; or b) if it is an imitation of, or is a substitute for, another drug or resembles another drug in a manner likely to deceive, or bears upon it or upon its label or container the name of another drug, unless it is plainly and conspicuously marked so as to reveal its true character and its lack of identity with such other drug; or c) if the label or container bears the name of an individual or company purporting to be the manufacture of the drug, which individual or company is fictitious or does not exist; or d) if it has been substituted wholly or in part by another drug or substance; or e) if it purports to be the product of a manufacturer of whom it is not truly a product.

The Food and Drug Administration, USA, defines counterfeit drug as :

"A drug which, or the container of which, or labelling of which, without authorization, bears the trademark, trade name, other identifying mark, imprint or device or any likeness, there of a drug manufacturer, processor, packer, or distributor other than the person, or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by such other drug manufacturer, processor, packer, or distributor."

According to WHO, a counterfeit medicine is one which, is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging

The term, "counterfeit" that is commonly used worldwide for spurious drug does not appear in Drugs and Cosmetics Act but the above definition of spurious drugs comprehensively covers counterfeit drugs also.

The Drugs and Cosmetics Act also defines "Misbranded Drug", under Section 17 and "Adulterated Drug", under Section 17A.

A drug is considered "Not of Standard Quality" or substandard if it fails to comply with any of the parameters of the overall standards laid down for it either in a recognized Pharmacopoeia or otherwise pre declared by the manufacturer.

Source: Mashelkar Committee Report (2003)

unscientific drugs. Restricting profit levels and the list of drugs that can be made in India to essential, scientific drugs could have considerably lessened the burden of testing and regulating. Are not irrational drugs a variety of spurious drugs? Are not high priced drugs killers of a kind, slowly but eventually immiserating the patient?

What's the Actual Situation on the Ground?[15]

According to Harinder Sikka, senior president, Nicholas Piramal, there are only 600 inspectors for 20,000 registered drug producers in the country.

In Delhi, for example, 20 inspectors are on duty for 8,000 registered chemist shops, which means one inspector for 400 shops. "The inspectors have obviously chosen the best way out. Concentrate on a few chosen chemists and improve your lifestyle," Sikka says tongue-in-cheek.

He, though, strongly defends the death penalty suggested by the Mashelkar committee and gives the example of a Chandigarh-based company that was using contaminated tap water instead of the drugs in vials.

The problem runs very deep indeed. There are over 20,000 registered drug producers in India who have been given the CGMP (certified good manufacturing practices) certificate. As many as 19,950 of the drug producers account for just Rs 10,000 crore (Rs 100 billion) turnover of the total Rs 22,000 crore (Rs 220 billion) annual turnover of the drug industry, while the balance 50 (big corporations) have a turnover of Rs 12,000 crore (Rs 120 billion).

Sikka has a simple question: "A majority of these manufacturers operate from garages and hovels. Who is renewing their CGMP licences?"

According to a report by Transparency International, bribes worth Rs 7,500 crore (Rs 75 billion) are paid in the health sector in India making it a win-win situation for all -- except the patient.

The profit margins are phenomenal. Sikka gives an example: an antibiotic that otherwise costs Rs 50 a strip is produced for less than Re 1 and sold to the distributor for Rs 10 ...

... Between the manufacturer and the retailer there lies a 5,000 per cent profit margin which provides adequate security against legal wrangles.

Over eight out of 10 drugs supplied by the government tested randomly proved to be spurious.

Studies done by non-governmental agencies have, in fact, shown that reusage of expired drugs is a flourishing racket in rural areas, which account for 40 per cent of the total sales of the drug industry.

This is despite the fact that expired drugs degenerate fast and in some cases are more harmful than even spurious drugs.

Paucity of Testing Laboratories

Only 17 States have drug testing (facilities) and even among these laboratories, only about 7 have the capacity to test all classes of drugs. On an average, about 36,000 samples are tested annually, both in the Central and State drug testing laboratories. The number is, however, inadequate as compared to number of batches of thousands of formulations manufactured in the country. Because of less capacity to test, the time taken to complete the testing of drug samples is observed to be taking even a year. This does not serve any purpose. As a result, samples of less than 1 % of the batches of drugs manufactured in the country are exposed to scrutiny by the Government drug testing laboratories. The number of samples that are reported every year as not of standard quality by the Central and State Government laboratories are only indicative of lax quality assurance system in the manufacturer's quality control labs and are not representative of the actual situation in the country. The limitations in testing of drug samples in the government labs are related to the absence or lack of sophisticated instruments, lack of trained analysts, lack of commitment, lack of reagents, non-validated methods, shortage of funds, inadequate number of staff and in many cases a combination of more than one of these constraints.

Source: Mashelkar Committee Report (2003)

5.2 Counterfeit Drugs: Terms of Discourse

What is a counterfeit drug? A counterfeit drug is defined differently in different countries. In order to address this problem the following definition has been developed by the World Health Organization:

"À counterfeit medicine is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging."

The problem of counterfeit drugs is known to exist in both developed and developing countries. However, the true extent of the problem is not really known since no global study has been carried out.[16]

The drugs counterfeited could include antibiotics, hormones, analgesics, steroids, and antihistamines. Counterfeit products can be grouped into at least six categories:

- Products without active ingredients
- Products with incorrect quantities of active ingredients
- Products with wrong ingredients
- Products with correct quantities of active ingredients but with fake packaging
- Copies of an original product
- Products with high levels of impurities and contaminants

Suffice it to say we need to distinguish the terms used in normal discourse, often interchangeably: terms like 'counterfeit', 'fake', 'substandard' drugs and 'poor quality' drugs. And drugs, which are copied without approval from the patent holder. Current laws in India prohibit counterfeit drugs in all the senses above. In some countries the issue is more complex and there is no distinction made between counterfeit and substandard drugs.

In developing countries, a wide spectrum of types of counterfeit drugs, ranging from the precise copy of a genuine product to the extreme case of a drug product with none of the correct active ingredients exist. Some include as counterfeit even unregistered drugs imported in the country, for other than personal use. Consequently, counterfeit drug is defined broadly in order to cover drug products that have been copied or forged as well as certain substandard products, particularly those intentionally made to be substandard.[17]

In a response to allegations by Harvey Bale, the Director General of the International Federation of Pharmaceutical Manufacturers Association (IFPMA), of copying and counterfeiting by India and Brazil, economist Bibek Debroy in a column in *Financial Express* pointed out:[18]

> … There is a difference between copying and counterfeiting. Copying is when you steal someone else's intellectual property and pass it off as your own. Counterfeiting is faking. You produce a product (incorporating intellectual property) that pretends to be someone else's. Your product is passed off as someone else's brand. Unfortunately, the word piracy is used for both copying and counterfeiting and this sometimes causes confusion ...
>
> …The (Indian) law may permit some varieties of copying. But counterfeiting is prohibited. In every country, including India … there are around 20,000 pharmaceutical producers in India. With such a

large, fragmented and heterogeneous industry, it is impossible to generalise. There are large (Indian) companies that are taking on the world (which is perhaps the reason IFPMA is upset) and there are producers who operate out of garages. Of course, there are sub-standard drugs in the market. Standards don't exist, or are hopelessly out of date, or are not enforced. Of course, there is copying. Of course, there are counterfeit drugs. But that's not what IFPMA is saying. IFPMA is tarring the entire Indian pharmaceutical industry with the same brush.

Take quality and assume for the moment that quality standards are non-existent in India. But the Indian pharmaceutical industry also exports. The present battle in the World Trade Organisation is primarily about African countries importing certain drugs from countries like India and Brazil.

India does export to Africa. However, India also exports drugs (and not just bulk drugs or drug intermediates) to the US as well and these have to comply with FDA (Food and Drug Administration) norms. I have been told, and IFPMA will correct me if I am wrong, that FDA norms are fairly stringent and not sub-standard. If that is true, it logically follows that the entire Indian pharmaceutical industry doesn't produce poor quality drugs. If American law is tough about counterfeiting, and the law is enforced, these exported drugs can't be counterfeit either. And since some Indian pharma companies have obtained patents in the US, these can't be the result of copying.

…. India has strengths in intellectual property, including pharmaceuticals. India doesn't need to copy. Counterfeiting has to stop and not because IFPMA thinks it should. … However, there is genuine concern about public health issues in several African countries. In the entire AIDS debate, the international pharmaceutical industry made a hash of public relations. If the IFPMA letter is any indication, industry hasn't learnt from that PR disaster.

Also what does one call the rush of me-too drugs put out by world pharma leaders, the drugs on which inadequate research is done, especially on effects of drugs marketed in children, old persons and women, and drugs for which new uses are found just to extend its patent period? Consider for instance what Dr Richard Nicholson, editor of the *Bulletin of Medical Ethics*, told the House of Commons Health Committee:

> A clinical trial was proposed to my ethics committee some years ago of Vioxx versus naproxen and we wondered to ourselves why on earth Merck want to compare this with naproxen. They did not give us the details initially and then when we asked and asked, we finally found out that they had already carried out major trials against the two major anti-inflammatory drugs … and found absolutely no advantage of their drug. They were hoping that by comparing it to naproxen, which had just five per cent of the market, they would be able to show an advantage.[19]

Counterfeit? In that case many of the leading Pharma companies in the world would stand accused of pushing counterfeit drugs.[20] And thriving.

5.3 Jekyll and Hyde Character of Indian Pharma Industry: Lentin, Nutraceuticals

Over the years, the pharma industry itself has been playing Jekyll and Hyde. Consider that the chairperson of the quality subcommittee of a leading industry association is the very person whose laboratory was indicted by the Justice Lentin Commission looking into the Glycol Tragedy of the late eighties. (See Annexure 1 for more details.)

Consider nutraceuticals, those products with nutrients and minerals, neither food nor drug, manufactured by drug companies and others, with curative and restorative claims on their labels. The worldwide market for nutraceutical products is estimated to be about 86 billion dollars with an annual growth rate of 17 percent. In the absence of scrutiny, the gullible public often buys them, many under advice of doctors. Some are very costly like the products made by Amway. Some even claim to alleviate serious ailments like diabetes, hypertension, arthritis, osteoporosis, etc. Industry is interested in this sector, as there are no adequate regulatory controls on their manufacture and marketing.

During October 2003, the First Nutraceutical Summit was held at Mumbai to crystallize proposals to be submitted to the government while framing a regulatory system, as at present no clear laws exist to regulate this burgeoning sector. "But when it came to the specific regulatory procedures to be suggested, most of the participants did not want even standard rules ensuring safety and efficacy of these products to be adopted. They wanted least possible regulatory interventions in key administrative areas. For instance, most participants were against conducting clinical trials in India for new ingredients used in nutraceuticals if the documentary support is submitted to the regulatory authorities. A second conclusion is that the permissions to market combinations of approved ingredients to be granted without clinical trials if the manufacturers can provide substantiation data. Most participants have opposed the suggestion to provide package inserts carrying consumer information about nutraceuticals. The participants also strongly opposed another suggestion seeking a ban on all forms of advertisements about nutraceuticals in the media. And the worst suggestion came from a leading Indian pharma company seeking to allow manufacturing of nutraceuticals in the same facilities where allopathic drugs are manufactured. Many opposed the idea but the company prevailed upon the organizers to include it part of the suggestions from the Summit. In short, the general mood of the participants was to have a regulatory system for the sector with no teeth."[21]

Spurious and Substandard Drugs Emanates from the Office of the Drugs Controller[22]

The following report shocking in its venality is from the relatively progressive state of Karnataka. It took a brave doctor to complain and a determined Lokayukta to investigate. How worse - or better - is the scenario in other states of India is anybody's guess.

- During February 2003, a medical doctor and activist belonging to the Drug Action Forum, Karnataka, lodged a complaint. A preliminary investigation revealed multiple irregularities.
- The office of the drugs controller (ODC) is mandated to ensure that only authorised drugs of specified quality are sold. Although over 249 drugs were tested and found to be sub-standard, the test results were available only after ten to 15 months. No action was taken to withdraw the sub-standard drugs from the market, nor was any action taken against the companies manufacturing these drugs. As a result, enough time passed for all the drug stocks to be sold.
- The ODC is responsible for controlling prices of essential drugs, 76 of which have been listed. However, it is estimated that the people of Karnataka paid almost Rs 200 crore in excess in the past year due to non-enforcement of price control orders by the ODC.

- The ODC is in charge of enforcing norms by granting licenses to drug manufacturers and retailers. In practice, those paying kickbacks were granted licenses circumventing norms through slight modifications in the composition of drugs, and other means. Those refusing to bribe, of which there were very few, were harassed.

The ODC grants licences for private blood banks. This was done with practically no monitoring or enforcement of standards. A private blood bank in Gulbarga supplied blood that was HIV-positive. Although a complaint was filed with the ODC, no action was taken.

Having observed these lapses, the KLA (Karnataka Lok Ayukta) called a meeting of over fifty officers. Some officers, banking on leniency for having co-operated with the KLA investigation, were vocal in exposing the corrupt practices. All the officers acknowledged that they were corrupt, but claimed that they had no choice. Each drugs inspector was required to hand over Rs 20,000 every six months to the drugs controller, who in turn gave it to the minister. Furthermore, the demands were increasing in frequency….

After further detailed investigation, by October 2003, Karnataka Lokayukta Justice N Venkatachala recommended the State Government order an inquiry into allegations of corruption and misconduct against three senior officials, including former State Drug Controller R Anandarajasekhar. In a report submitted to the Government, the Lokayukta stated that Anandarajashekar, Additional Drugs Controller H Jayaram and Deputy Drugs Controller B G Prabhakar (Blood Bank and Intelligence) were found prima facie guilty of corruption and gross misconduct.

"Not only disciplinary action is required to be taken against all of them jointly and severally, but they also have to be made to vacate the offices held by them at the first instance," the report stated. "In the interest of freeing the administration of the State from government servants, who are prima facie guilty of gross misconduct and corruption and could be found finally guilty of gross misconduct and corruption in the disciplinary inquiry to be held against them, the Government needs to issue an appropriate order immediately under the Karnataka Lokayukta Act," the Lokayukta said.

With reference to serious violations by these officials, the Lokayukta said they had failed to perform their statutory and administrative responsibilities of getting the licensed manufacturing units inspected twice a year and had also failed to initiate prosecution against drug manufacturers in Karnataka and other states who were manufacturing "substandard, adulterated, spurious and misbranded drugs."

These officials had also failed to take action against chemists and druggists in the State for selling scheduled drugs and "habit forming" drugs without prescription, the report stated.

In the next chapter we examine other aspects of drug marketing: drug promotion, clinical trials and conflicts of interest: the unfortunate nexus, some willing and some unintended, between the drug industry and the medical profession.

Annexure1

Landmark Incidents in the Unethical Marketing of Drugs

SMON Tragedy in Japan

Clioquinol, a widely used, over-the-counter drug for the treatment of traveller's diarrhoea is marketed as Mexaform, Entero-Vioform, Enter-Quinol, etc. However there is very little evidence that it is effective against this disorder. In fact it is known to cause subacute myelo-optic neuropathy (SMON), a serious side-effect affecting the nervous system, causing damage to the spinal cords and the nerves, including the optic nerve.

In 1970s, approximately 11,000 Japanese were victims of SMON. When it was clearly established that SMON was caused by the drug clioquinol, they undertook legal action against the drug company, Ciba-Geigy, which has its headquarters in Basel, Switzerland.

SMON litigation began in May 1971 in Tokyo. Ciba-Geigy responded with the statement, "the SMON problem is a peculiarly Japanese one and they were not responsible to Japanese patients." However, Ciba-Geigy was responsible because it is a multinational company and Ciba-Geigy (Japan) is its subsidiary. The head office is 100 per cent stockholder of the Japanese subsidiary and Mr. Planta, the president of Ciba-Geigy in Basel is the director of Ciba-Geigy (Japan).

A world-wide study, undertaken by the International Organization of Consumers Unions, of clioquinol, its brand names and information accompanying the drug, found vast differences in drug information. Ciba-Geigy's Entero-Vioform manufactured in Switzerland, as sold there and as exported to Greece, Portugal, Kenya, South Africa, Hong Kong, Malaysia and Singapore, limited the maximum dosage to 750 mg, listed the four main contraindications - hyperthyroidism, iodine allergy and impaired liver or kidney function; mentioned the side-effects, peripheral and optic neuritis, and warning to stop the drug at the first signs of abnormal sensations and visual disturbances. However, when exported from Switzerland to Thailand and Indonesia the instructions specified a maximum dose of 1500 mg, omitted malfunctioning of liver or kidneys from the list of contraindications and failed to warn the user to stop the drug at the first signs of neuritis. Similarly, Entero-Vioform manufactured in UK, as sold there and as exported to Bahamas, Belize, and New Zealand limited the course of treatment to a total of 3 g (1000 mg for 3 days). On the other hand, when exported to Tanzania their instructions specified a maximum of 15 g. Tanzanians now got their Entero-Vioform from Switzerland, with a maximum course of treatment for chronic diarrhoea specified as 21 g. Why Ciba-Geigy maintained different sets of cautionary information for different countries could be explained because drug regulatory authorities in some countries did not require manufacturers to conform to guidelines concerning the use of clioquinol. All the same this double standard on the part of Ciba-Geigy was unconscionable.

As Ciba-Geigy continued to market clioquinol inspite of known hazards and doubtful hazards, 3000 Swedish doctors boycotted Ciba-Geigy products, causing the company to lose 25% of its market in Sweden. In August 1978, the Tokyo District Court ruled in favour of the SMON victims and ordered Ciba-Geigy to make a settlement which will adequately compensate for their sufferings and to submit an apology to the SMON victims. The Court noted:

"The Ciba-Geigy head office in Basel investigated reports that dogs given Entero-Vioform or Mexaform often developed epileptic seizures and died, and the company circulated a warning among veterinarians not to use these drugs in veterinary treatment. However, although 'these drugs were produced for human use', they not only did not take any measures to warn about the dangers of use by humans, but also, they continued to stress thereafter the safety of Entero-Vioform and Mexaform and Mexaform in Japan, which can be considered deplorable.

"If Ciba-Geigy had taken the appropriate measures at that time, it is probable that the suffering of most or at least a considerable number of SMON patients could have been avoided. Under such conditions, this must be considered as a matter of deep regret with respect to the Defendant Ciba-Geigy."

Ciba-Geigy in its written apology stated "... [the plaintiffs'] grievances were all earnest expressions of their pain, distress, and anger; appeals were made for redress. They were heart rending cries that made us realize anew that SMON has caused the patients and their families unimaginable suffering ... In view of the fact that medical products manufactured and sold by us have been responsible for the occurrence of this tragedy in Japan, we extend our apologies, frankly and without reservation to the Plaintiffs and their families ... We have also realized, with regret, that when recently asked the court to act as mediator we neglected to adequately express our sincerity. Again, we deeply apologise to the plaintiffs and their families."

Lentin Commission Report

In 1986, 14 patients died of acute renal failure at the J. J. Hospital in Bombay after being administered glycerol adulterated with diethylene glycol.

The one-man Justice Lentin Commission was set up by the Maharastra Government to investigate the reasons for this tragedy.

The Commission, over a period of 17 months, sifted through numerous files, cross-examined 120 witnesses and exposed the nexus between politicians, the Food and Drugs Administration (FDA) and the drug manufacturers. It revealed the protection these manufacturers received from FDA, the flagrant violation of laws in issuing licences, deferring prosecution of errant manufacturers and ministerial interference at every stage.

It was found that the adulterated glycerol which is meant for industrial use was supplied by Alpana Pharma, whose tender to supply had been accepted by the Tender Committee, in gross violation of several rules of acceptance of tender. In addition, Chem Med Lab had given a quality control report stating the drug to be of standard quality without even conducting the requisite tests. And most horrendous of all,

even after the killer drug was more or less identified, it continued to be administered due to negligence of those concerned.

The Commission revealed some startling facts:

- 300 formulations were found to be sub-standard between February and July 1987, yet they continued to be sold.
- 20 per cent of drug samples were found to be substandard, yet the FDA made no attempt at follow-up action.
- Several summons to the State Government and FDA to produce a missing file evoked no response.

When a newspaper reporter finally unearthed the file, it contained evidence of FDA manipulations to pass a drug formulation manufactured by Glindia (Glaxo Laboratories) which was not of standard quality.

The outcome of the Lentin Commission Report may not have been spectacular. Some heads may have rolled and some minor cosmetic change may have been made. Prior to the publication of the Commission Report, the Health Minister, Bhai Sawant resigned saying the Commission had drawn unpermissible conclusions. In an unprecedented show of solidarity, MLAs from the opposition and the ruling party joined hands in criticising the Commission's findings regarding the role of the politicians in the glycerol scandal. Indeed one opposition MLA even raised a notice of breach of privilege against Justice Lentin. However the Lentin Commission has atlast made public what was always suspected - the rot which has set in the public health care system and the drug administration, and the corruption of high-level officials, ministers and the drug industry.

EP Drug

High-dose estrogen-progesterone (EP) combination drugs contain the same female sex hormones as the combined oral contraceptive pill but at a higher level. These drugs were used in 1950s as a treatment for missed periods since they were thought to start menstruation in women whose periods were delayed and who were not pregnant. A woman whose periods did not start after taking EP drugs was presumed to be pregnant, and hence EP drugs were used for pregnancy testing. But because the drug could apparently bring on menstruation, EP drugs were misused to induce abortion. Although no pharmaceutical company has ever claimed that these drugs will induce abortion, there was evidence in India that they were prescribed by doctors for this purpose and were also sold over the counter. About 20 years later, research uncovered evidence that the EP drugs were unreliable as pregnancy tests and ineffective as treatment for missed periods. In fact evidence showed that the drugs were associated with birth defects. Those women who used this drug for pregnancy testing and continued with their pregnancy exposed their unborn babies to the possibility of birth defects. Those women who took the drug to induce abortion but did not abort, also ran the same risk, Many countries began to withdraw this drug since 1970. In India the drug was used for a variety of disorders and by 1982, an estimated 180,000 were using the drug each year.

Indian health and consumer groups launched a campaign for the withdrawal of this drug and as a result a warning was added in the drug information insert, "Not to be used for pregnancy test and suspected cases of pregnancy". In June 1992, the Drug Controller of India banned the manufacture of all EP formulations effective from 31 December 1982, and its sale from 30 June 1983. The ban was severely criticised because

though it was considered hazardous enough to be banned, yet it was allowed to be sold for another six months simply so the stocks would finish. However two pharmaceutical companies Unichem and Nicholas contested the ban. Infar, the Indian subsidiary of the Dutch pharmaceutical company, Organon, which is not allowed to manufacture and sell the product in its home country, filed a petition against the ban. Their arguments covered various aspects of the ban: the legalities, drug misuse, hazards and medical details. As a result in January 1983, a stay order against the ban and a two-year extension of the product license was granted by the Calcutta and Bombay High Courts on legal technicalities. The ban was thus effectively stalled by the stay order. This meant that till the case came up for trial, the hazardous drugs could be manufactured and sold in the country. Appalled by this decision, various health and consumer organisations continued the campaign and after five years of relentless struggle, they succeeded when in 1988, the Indian government banned the manufacture and sale of high-dose combination of EP "containing per tablet estrogen content of more than 50 micrograms and of progesterone content of more than 30 milligrams". This decision was particularly welcome when safer alternatives and non-drug methods for pregnancy testing are available in the country.

Depo Provera and Injectable Contraceptives: Disturbing Side-effects

Dr. C. Sathyamala's book. *An Epidemiological Review of the Injectable Contraceptive*, Depo Provera (Pune/Mumbai: Medico Friend Circle and Forum for Women's Health, 2000) is required reading for anybody intrested in injectable contraceptives, whichever side of the debate one tends to be. At the end of her carefully argued monograph, she concludes:

> ... The weight of evidence relating to the hazardous nature of Depo Provera is sufficient to compel its proponents to admit to the injectable's potential for adverse outcomes including death. However, the issue is side-stepped and the relatively high maternal mortality in developing countries is cited as reasons for differing risk-benefit assessment for use in developed and not so-developed countries (WHO, 1982; Chilvers, 1994).
>
> While it is debatable whether high contraceptive prevalence alone as a single measure will reduce mortality and morbidity posed by pregnancy related causes, in the context of the third world countries, three points need to be remembered: Firstly, the population at risk of pregnancy may be different from the population at risk of contraception; secondly, the contraceptive risks may be an added on risk to pregnancy risks; and thirdly, the very factors that are responsible for the high obstetric deaths in a developing country would increase deaths due to Depo Provera use.
>
> The review of literature presented in this monograph is to enable the reader to weigh the risks and benefits of the use of Depo Provera as a temporary method of contraception in women from the disadvantaged sections of society.
>
> Depo Provera appears to be hazardous to the health of the women and her progeny. The contraceptive appears to be not suitable for nulliparous women, adolescents, breast feeding women, women who have not completed their family, and women who are in the reproductive age group. In short, there does not seem to be a single group of women for whom Depo Provera can be safely recommended as a contraceptive method of choice ...

On the other side, Dr. R. P. Soonawalla, eminent gynaecologist of Mumbai and Principal Investigator, Post Marketing Surveillance Study of Depo Provera, has this to say (interview, *The Hindustan Times*, May 22, 1994, quoted in Sathyamala, op. cit.):

> ... I am saying, let it (Depo Provera) be available. Nobody is forcing anybody to take it. Let the doctor decide what is right for the patient. Obviously, the doctor will monitor its use and if there are problems, no doctor or patient is foolish enough to continue its use.
>
> Why should it be banned, and why should we have to smuggle it for our patients? Who are these women who are protesting against it? Ill-informed, so-called feminists, who are just a bunch of college girls with nothing better to do. Without going into the issue they are making a noise about it. Barging into meetings, carrying placards, shouting slogans. There are so many important issues that need attention. Why don't they do something about slum children dying or about the blind?
>
> They say that the first world is trying to foist it on the third world women. This is rubbish. A lot of life-saving drugs came to us after being formulated and tested in the West, they didn't object to those, but here they have a platform to make a lot of noise and hullabaloo about nothing. What kind of ethics are these? For atleast the next decade there won't be a perfect contraceptive. Every drug has some side-effects. It is up to the doctor and the patient to decide what is the best method. My only concern is for my patients ....
>
> .... Calling for a ban on Depo Provera is like the anti-abortion protests, which want to take away the choice from women. I have come across so many cases of women who publicly opposed abortions, but quietly went and had abortions done. I am sure a lot of women who are opposing Depo Provera will take the injections themselves. It is alright to be clever when it comes to other people. They have no right to dictate to responsible doctors what they should or should not prescribe to their patients. If there are a few black sheep, pick on them, don't deprive everybody else of the use of a particular drug, especially when all research has proved these contraceptives to be safe...

A third opinion runs something like this: in view of Depo's disturbing side-effects, it may not be introduced in the Government's Family Welfare Programme, as it is target-oriented and therefore it may be imposed on innocent women without checking for contraindications or otherwise properly explaining to the user. The Indian Public Health system is not geared to meet the need of close followup and monitoring that the use of Depo requires. Thus Depo Provera may be used for 'private marketing'. As of today Depo is available against prescription and is not included in the Government of India's Family Welfare programme.

However, Net-en, another contraceptive with equally disturbing side-effects, is being introduced in the official family welfare programme in "such places where adequate facilities for followup and counselling are available" (affidavit filed by Ministry of Health and Family Welfare on August 18, 2000 in the Supreme Court of India in the matter of Stree Shakti Sanghatana and Others versus the Union of India and Others). What is the real danger of either injectable contraceptive being misused or used in the wrong situation is anybody's guess.

The Thalidomide Children and the Law

The thalidomide babies have grown up. It is 11 years since the deformities they suffer shocked the world. Some 8,000 mothers who took the drug bore deformed children, 400 or so in Britain. Many people must long ago have assumed that society had paid its debt to the children and the parents; few can fail to recall the wave of compassion and anger that followed their birth. Yet even now the bulk of the compensation claims in Britain are not settled, and the peculiar agony of this saga is that no one should feel a sense of relief that at last a settlement may be in sight. One should feel only a sense of shame.

First, it shames our society that a decade has passed. No money can ever compensate for being a limbless trunk, but at least a generous compensation can give the glimmer of a normal life. One thinks also of the parents who for so long have had added to their sorrows the anxieties of protracted litigation.

Secondly, it shames the law that the compensation proposed should be so low ..... Essentially Mr. Justice Hinchcliffe fixed the level when in two test cases in 1968 he assessed what the damages would be if the drug's seller, Distillers Biochemicals, lost a suit for negligence. Distillers agreed to pay 40 per cent of the assessment if the allegations of negligence were withdrawn. Clearly, if the full sum was judged "sufficient" to compensate the victims, the 40 per cent must be judged 60 per cent insufficient to human need at the time, to say nothing of the effects of future inflation. Even the full sum exposes the crudeness of the rule-of-thumb assessments of the law. As the Law Commissioners say, the legal method of fixing damages lacks any mathematical actuarial, statistical or other scientific basis. What is stopping the Government immediately bringing in an Act to make evidence of this kind crucial?

Thirdly, the thalidomide children shame Distillers. It is appreciated that Distillers have always denied negligence and that if the cases were pursued, the children might end up with nothing. It is appreciated that Distillers' lawyers have a professional duty to secure the best terms for their clients. But at the end of the day what is to be paid in settlement is the decision of Distillers, and they should offer much, much more to every one of the thalidomide victims. It may be argued that Distillers have a duty to their shareholders and that, having taken account of skilled legal advice, the terms are just. But the law is not always the same as justice. There are times when insistence on the letter of the law is as exposed to criticism as infringement of another's legal rights. The figure in the proposed settlement is to be £3.25m, spread over 10 years. This does not shine as a beacon against pre-tax profits last year of £64.8 million and company assets worth £421 million. Without in any way surrendering on negligence, Distillers could and should think again.

And the Government must act. The adversary system will not do. Compassion after disaster requires a state insurance scheme for compensation, as some have long advocated for personal injury cases. But even the wisest reform will be a sham if society does not now insist on justice for the victims of an enduring tragedy.

Source : *The Sunday Times*, Sept 24, 1972. Quoted in *The Thalidomide Children and the Law*, Andre Deutsch, London, 1973.

Endnotes

[1] Source: < http://www.freedoniagroup.com/World-Pharmaceutical-Packaging.html>

[2] See Chapter 4, "Pharma Pricing in India: A "Failure of theMarket(s)?" in *Impoverishing the Poor: Pharmaceuticals and Drug Pricing in India*. LOCOST/JSS, Vadodara/Bilaspur, December 2004. Here after referred to as *Impoverishing the Poor*.

[3] Figures quoted from NSSO and background papers, "Financing and Delivery of Health Care Services in India" of the Report of the National Commission on Macroeconomics and Health, Sep 2005.

[4] For more details, see *Impoverishing the Poor*. This section is taken from the same and authored by Anurag Bhargava.

[5] Comment by Matthew Herper "The World's Best-Selling Drugs" at < http://www.forbes.com/2004/03/16/cx_mh_0316bestselling_print.html>

[6] Reproduced with permission.

[7] For more details see, *Impoverishing the Poor*.

[8] The text that follows has to be read in the context of other distortions discussed in other chapters in this book.

[9] Quoted in "Changing Era of Social Responsibility and Corporate Ethics in Indian Pharmaceutical Industry" by Indurkar at <http://www.aims.org.in/aims/articles/Theme%20I%20-%20Corporate%20Values%20&%20Ethics/AIMS-IndurkarPAPER%2001.doc>

[10] 'Cape Town study faults Lupin's TB drugs'

[11] Singh, Jagvir, Dutta, A.K., Khare, Shashi et al. Diethylene glycol poisoning in Gurgaon, India, 1998. *Bull World Health Organ*. [online]. 2001, vol.79, no.2, pp. .88-95. Available on the Web: <http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S0042-96862001000200002&lng=en&nrm=iso> at <http://www.expresshealthcaremgmt.com/20020731/edit4.shtml>

[12] "Belittling of a High Office" June 27, 2000, Editorial, <www.pharmabiz.com>

[13] See "Study on Haematinic Formulations Marketed in India", *BODHI*, Vol 10, No 2, May-June 2002

[14] See 1) "Harmonisation and intellectual property: What impact would "harmonisation" have on developing country regulators?" at <http://www.eldis.org/healthsystems/regulation/harmonisation.htm>.
2)Hill, S.; Johnson, K. "Emerging challenges and opportunities in drug registration and regulation in developing countries". Department for International Development Health Systems Resource Centre (DFID HSRC), 2004.
3) Abraham, John. "Pharmaceuticals, the state and the global harmonisation process." *Aust Health Rev* 2004; 28 (2): 150-160.
4) "WHO BENEFITS: International Harmonisation of the Regulation of New Pharmaceutical Drugs" at website of Women and Health Protection , <http://www.whp-apsf.ca/en/documents/who_benefits.html#n6>

[15] "An overdose of intention", September 15, 2003 at <http://www.rediff.com/money/2003/sep/15guest.htm>

[16] For WHO perspective on counterfeit medicines, see <http://www.who.int/medicines/services/counterfeit/overview/en/>. The website says: "The United States Food and Drug Administration estimates that counterfeits make up more than 10% of the global medicines market and are present in both industrialized and developing countries. It is estimated that up to 25% of the medicines consumed in poor countries are counterfeit or substandard. These figures place the annual earnings from the sales of counterfeit and substandard medicines at over US$ 32 billion globally. Trade in these medicines is more prevalent in countries with weak drug regulation control and enforcement, scarcity and/or erratic supply of basic medicines, unregulated markets and unaffordable prices. However, one of the most counterfeited drugs today is Viagra, which is sold extensively via the Internet in industrialized countries. A World Health Organization (WHO) survey of counterfeit medicine reports from 20 countries between January 1999 to October 2000 found that 60% of counterfeit medicine cases occurred in poor countries and 40% in industralized countries."

[17] See also "Guidelines for the development of measures to combat counterfeit medicines' at <http://www.who.int/entity/medicines/publications/counterfeitguidelines/en/index.html>.
See also the proceedings of a recent WHO conference "Combating Counterfeit Drugs: Building Effective International Collaboration," 16-18 February 2006 - Rome, Italy. Details at <http://www.who.int/medicines/counterfeit_conference/en/>

[18] Source: <http://www.financialexpress.com/columnists/full_column.php?content_id=27319>

[19] House of Commons Health Committee. *The Influence of the Pharmaceutical Industry, Volume* I, Report, together with formal minutes. Fourth Report of Session 2004-05. Available at <www.parliament.uk/parliamentary_committees/health_committee.cfm>.

[20] See also for instance Chapter 6, "How Good Are New Drugs?" in Angell, Marcia. *The Truth About the Drug Companies: How they deceive us and what they do about it*. Random House, New York, 2004.

[21] "A Law For Nutraceuticals", October 15, 2003 Editorial by P A Francis in <http://www.pharmabiz.com>. See also "Prescribing Dietary/Nutritional Supplements: Where is the Evidence?" in *BODHI*, Vol 9, No 2, July-Aug 2002.

[22] Source:Dr H Sudharshan, personal communication, and <http://www.humanscapeindia.net/humanscape/new/october03/smallsteps.htm> <Http://www.newindpress.com/Newsitems.asp?ID=IEK20030930140411&Title=Southern+News+-+Karnataka&rLink=0>

Chapter 5

Drug Promotion, Clinical Trials, and Conflicts of Interest

"Gifts buy you time with a doc, time that might change his mind. . . .Money is the big resource. The pads and pens are great for access, but the dinners and what costs money. CDs, handheld computers, everything given in the name of research this is what's thrown at docs to get them to change their minds." A Former Detailer

Drug industry lobbies do not appreciate people who squeal, the outstanding instance is the documented case by Stanley Adams in his book *Roche Versus Adams.*[1] Stanley Adams was an executive who did what he felt was right by alerting the European Commission to cartelisation and anti-competitive practices by Swiss-based pharmaceutical giant Hoffmann-La Roche. The Commission fined Hoffmann for abuse of its dominant position in the bulk vitamin market but during antitrust proceedings disclosed information that enabled Hoffmann to identify Adams, who was consequently arrested and convicted for unauthorised disclosure under Swiss law. Adams was hounded by Swiss law, arrested while crossing the borders, and thereafter things went horribly wrong for him and his family including the 'suicide' of his wife. Adams successfully sought damages from the Commission, which was held by the European Court to have failed its obligation "not to disclose information of the kind covered by the obligation of professional secrecy, in particular information about undertakings, their business relations or their cost components." In 1999, Roche was fined US $500 million in the US for a repeat of its offence.

A more recent instance is that of cardiologist Dr. Eric Topol. Within a week of his testifying against Merck he was deprived of his position as chief academic officer at Cleveland Clinic's Medical College.[2] His demotion immediately after he lambasted Merck in a videotaped testimony, in the third Vioxx (rofecoxib) lawsuit to reach trial, was too much of a coincidence. Dr. Topol had questioned Vioxx's safety for years and said in his testimony, played in court, that he believed that Merck acted irresponsibly and committed scientific misconduct when it promoted Vioxx.

For those who want to play ball, the game starts with forms of entanglement right from the intern stage, later blossoming into cozy connections. We discuss these in this chapter and how it affects patients.

1. "Forms of Entanglement"

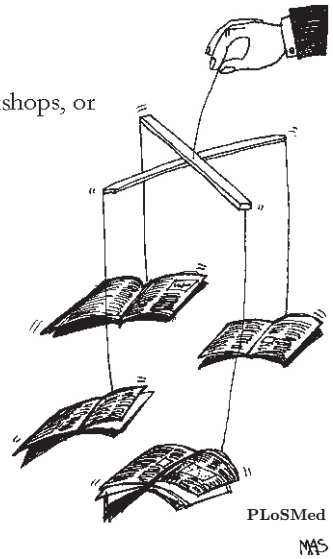
World over, and in India specifically, medicines are promoted by all means fair and foul. It is understandable, to some extent, that pharma companies aggressively market their drugs; and persuade doctors by a variety of means. But it is not clear why doctors should pretend that such marketing does not influence their prescribing behaviour and therefore it is okay not to resist the marketing overtures of drug companies.

Drug promotion is carried out by means of heavy advertising, frequent visits to private medical practitioners by the medical representatives of pharmaceutical companies with literature on their drugs,

free sample of drugs, and even blatant bribes like diaries, posters, calendars, pens, or other gifts, and sometimes also invitations to medical conferences held in five-star hotels with lavish meals and expensive give-aways. Drug companies also encourage articles in newspapers and magazines, television and radio programmes, release promotional materials as news stories about latest developments in medical field and sponsor television programmes. Thus, drug promotion is a comprehensive attempt to influence health workers and the general public to suspend their critical judgment.[3] (See box on *Forms of Entanglement* and also box on *Opinions of International Panel on Drugs Advertised in Indian edition of BMJ.*)

Forms of Entanglement:Who pays for the Pizza?[4]

- Face to face visits from drug company representatives
- Acceptance of direct gifts of equipment, travel, or accommodation
- Acceptance of indirect gifts, through sponsorship of software or travel
- Attendance at sponsored dinners and social or recreational events
- Attendance at sponsored educational events, continuing medical education, workshops, or seminars
- Attendance at sponsored scientific conferences
- Ownership of stock or equity holdings
- Conducting sponsored research
- Company funding for medical schools, academic chairs, or lecture halls
- Membership of sponsored professional societies and associations
- Advising a sponsored disease foundation or patients' group
- Involvement with or use of sponsored clinical guidelines
- Undertaking paid consultancy work for companies
- Membership of company advisory boards of "thought leaders" or "speakers' bureaux"
- Authoring "ghostwritten" scientific articles
- Medical journals' reliance on drug company advertising, company purchased reprints, and sponsored supplements

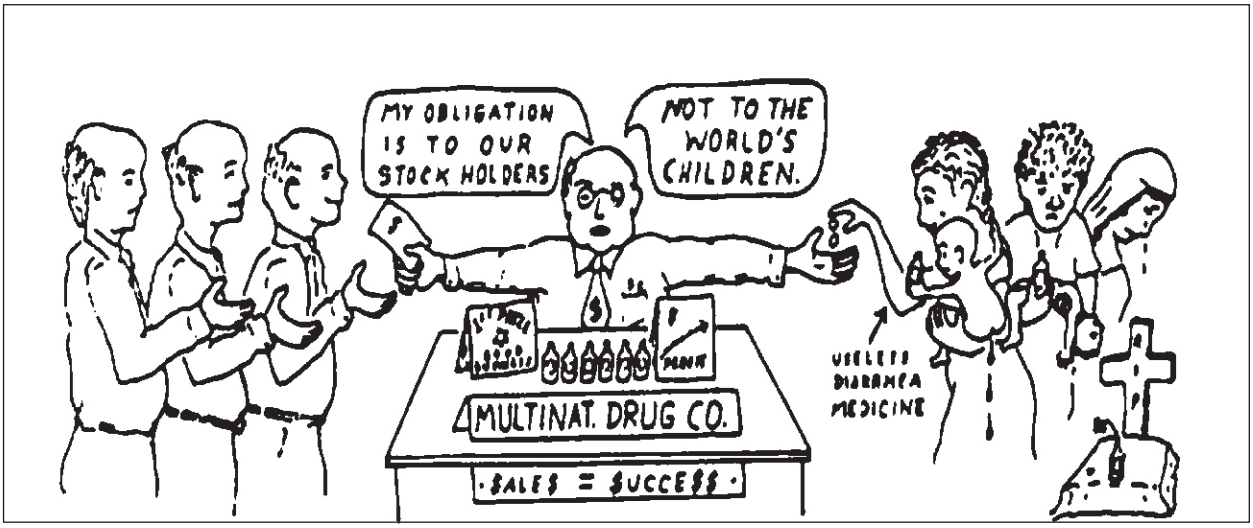


A senior professor of medicine of the prestigious Government of India post-graduate institute, JIPMER, Pondicherry, in a response to a *BMJ* editorial,[5] "Marketing of Medicines in India: Informing, influencing or inducing?," wrote: "In India and several other countries, the marketing ploys include an upgraded 5-C technique: 1. Convince by facts and figures 2. Confuse by misrepresenting data or using junk data 3. Coax by appealing to pragmatism: "All said and done Doctor, your patients expect you to prescribe..." 4. Corrupt and (if that fails - it does with upright Doctors even today) 5. Cry (usually a sob story of the plight of being a sales executive with a target to meet or else...). Several of my friends experience the 5-C ploy all the time. Infact we have made a video role-play to sensitise our undergraduate medical students on how to face up to the 5-C challenge."

Opinions of International Panel on Drugs Advertised in Indian Edition of BMJ [6]

- Trental 400 (pentoxifylline): "The advertisement makes unsubstantiated claims of improvement in mental function." (This drug is marketed only for peripheral vascular disease in America and Britain; in India it is indicated for cerebrovascular disease as well.)
- Relaxyl (diclofenac): "The claim 'gentle on the gastrointestinal tract' is not in accord with the reported high incidence of gastrointestinal side effects (up to 30% in Australian approved product information)."
- Alarsin products (Indian preparation): "There is no information on active constituents, side-effects, or contraindications, and the claims made are unsubstantiated."
- Keflor (kefaclor): "Makes unsubstantiated claims such as 'respiratory specific.'"
- Fludac (fluoxetine): "This advertisement distorts the side-effect profile by mentioning only the advantages it has over tricyclic antidepressants. There is no information on contraindications or dosage."
- Globac (haemoglobin ferric ammonium citrate, copper sulphate, manganese sulphate, zinc sulphate): "No evidence for therapeutic effect is given, and there are no clear indications for use."
- Mentat (Indian preparation): "There is no information on constituents, indications, precautions, or dosage. There is no evidence given for clinical efficacy, and the reference is to a study in an obscure (in house) journal."
- Ciprodac (ciprofloxacin): "The claim 'super power in your hands' is meaningless. There is no mention of the generic name, constituents, contraindications, or side-effects."
- Ciprowin (ciprofloxacin): "Makes unsubstantiated superlative claims such as 'surgical infections: most effective and cost effective therapy' and 'LRTI: better than third generation cephalosporins.'"
- Ciprobid (ciprofloxacin): "The claim 'superior to chloramphenicol, aminoglycosides, cephalosporins in ... bronchopneumonia, osteomyelitis' is misleading."

(Just to give an idea of the detail a drug company goes to influence a doctor, in the following three pages, Exhibits 1-2, we give Merck's instructions to its sales force on how to obfuscate when the Vioxx debacle was just rolling in. For other related documents see <http://reform.house.gov/GovReform/Hearings/> on Vioxx.)



David Werner

Exhibit 1

MERCK

MEMO

TO: All RBG VPs and Senior Business Directors

FROM: MIT for Vioxx®

SUBJECT: Offensive Positioning for Vioxx® DATE: 07/28/00

In order to win the on-going COXIB battle, many of you agree our sales force needs to STOP defending Vioxx® against the outrageous claims from our competitors, and START offensively selling the core benefit of this product...EFFICACY.

It is evident that Pharmacia/Pfizer will continue to concentrate their selling efforts on building a perception around renal and hypertension issues with Vioxx®. In order to put these issues into perspective so that our Representatives can transition their discussion to our Top 5 messages for Vioxx®, the Point Business Directors for Vioxx® have requested the TBG and MIT provide a "quick hit" reply to aid Representatives in this transition.

The components of a "quick hit" proactive Vioxx discussion should include the following:

- A "quick hit" response to the renal/hypertension obstacles
- Top 5 Messages for Vioxx®
- A STRONG close to prescribe Vioxx®
- A "closing question" to put the Celebrex® Representative on the defensive

Attached is a suggested communication flow for Vioxx® which includes the "quick hit" response to the renal/hypertension obstacle and effectively transitions to the Top 5 messages.

See attachment "A"

If the renal/hypertension obstacle is not initiated by a physician at the beginning of a discussion, this is where a Representative should proactively initiate a HI COXIB or HI NSAID discussion based on the physician flag.

As previously discussed on the Point Business Director teleconference on July 15, by moving to this proactive positioning with Vioxx® now, we will maximize our opportunity for market leadership which will be further supported by the OA comparative data to be released within 3T.

Confidential - Subject To Protective Order

Exhibit 1 (contd.)

If the doctor requests further clarification regarding the renal effects of VIOXX, use the Renal Card in accordance with the Renal Card Roadmap to address the physicians concerns. Once addressing the physicians concerns, move to the CLOSE.

CLOSE: Dr., based on the efficacy, safety and convenience of Vioxx, is there any reason why you wouldn't chose Vioxx first for your approporate OA and acute pain patients?

As you leave, use one of the following questions:
Doctor, one last thing, ask your Celebrex representative:

1. In the AE table of the Celebrex prescribing information, doesn't it state that the rate of edema with Celebrex was more than double that of ibuprofen 800 t.i.d.?
2. " How do I manage my OA patients who don't achieve relief from Celebrex 200mg daily?"

Answers to these questions:

1. The AE table in the prescribing information for Celebrex states shows the rate of edema for Celebrex was more than double the rate for ibuprofen 800 t.i.d. Of interest, the AE table for Vioxx states the rate of edema for Vioxx was less than that of ibuprofen 800 t.i.d.,

2. According to the Prescribing Information for Celebrex, in patients with OA, treatment with Celebrex 100 mg BID or 200 mg QD resulted in improvement in WOMAC osteoarthritis index. **Doses of 200 mg BID provided no additional benefit above that seen with 100 mg BID.** Therefore, it seems as if double the dose of Celebrex offers no additional benefit, yet doubles the cost.

Confidential - Subject To Protective Order

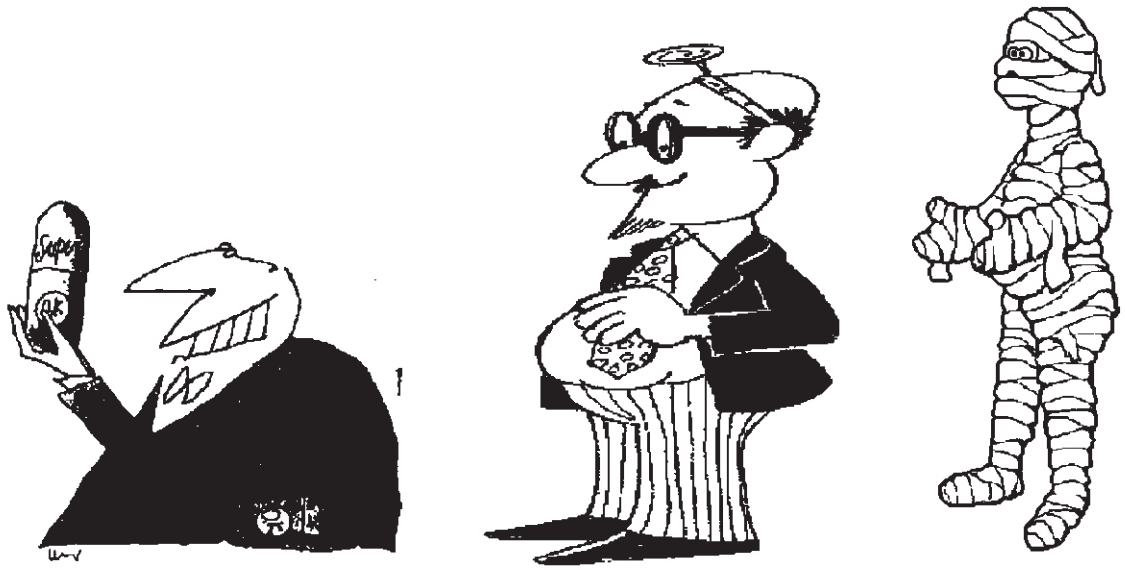


Exhibit 2

ATTACHMENT "A"

"QUICK HIT" Communication Flow

If the doctor first mentions concern with hypertension and edema, use the following "quick hit" reply, otherwise, begin with an offensive HI COXIB or HI NSAID discussion:

Doctor, is your concern based on personal experience or due to comments from the competition? Doctor, the competition would like you to believe that there are issues with hypertension and edema unique to VIOXX. However, in OA clinical trials, the incidences of hypertension and edema with VIOXX were comparable to those seen with both ibuprofen and diclofenac. The renal effects of VIOXX are no different than any other NSAID.

Deliver the following offensive HI COXIB detail:

Let me tell you why VIOXX should be your first choice, over Celebrex, for appropriate OA and acute pain patients.

First, **VIOXX provides ONCE DAILY POWER in chronic OA.** VIOXX 12.5 and 25mg, once daily, provides relief which lasts all day, all night, and into the next morning. This powerful relief which VIOXX offers your OA patients was shown in studies lasting one year.

Second, **VIOXX is the only COX-2 targeted agent that reduced the need for rescue narcotic analgesia in post-orthopedic acute pain studies.** The ONCE DAILY POWER of VIOXX in acute pain was consistently demonstrated in all models studied: post orthopedic surgical pain, postoperative dental pain, and primary dysmenorrhea. Celebrex has failed similar post-surgical pain models and was denied an acute indication by the FDA. You can count on VIOXX to deliver **ONCE DAILY POWER** for your OA and acute pain patients.

Third, **unlike Celebrex, VIOXX is not contraindicated in patients with sulfonamide allergies.** This benefit provides one less concern for you when choosing a medication for your OA or acute pain patients. Choose VIOXX first.

Fourth, **the safety profile of VIOXX was demonstrated in patients 80 years or older.** In addition, over 40% of patients in clinical trials for VIOXX were greater than 65 years of age, and there was no substantial difference in safety between younger and older patients.

Doctor, along with the ONCE DAILY POWER and safety which VIOXX offers you and your patients, there is one last thing that I want you to remember, **VIOXX is the only COX-2 targeted agent that offers the SAME PRICE for either dose in OA.** Since 45% of patients taking Celebrex for OA are prescribed a b.i.d. dose, VIOXX offers the majority of patients a cost advantage over Celebrex. (Use the Utilization Card to support this message) Also, not only is VIOXX the least expensive COXIB, VIOXX is the least expensive branded NSAID.

Trial Close: Doctor, has this information provided enough reasons for you to prescribe VIOXX for appropriate OA and acute pain patients?

A more recent *Time* magazine[7] article reporting on the No-Free Lunch campaign[8] launched in the US had this to say:[9]

"For decades, taking gifts from drug makers has been business as usual for doctors. The pharmaceutical industry spent $22 billion on marketing to physicians (including free samples) in 2003, up from $12.1 billion in 1999, according to data from Pharmaceutical Research and Manufacturers of America (PhRMA). The industry is on track to spend almost $3 billion in 2005 solely on meetings and events for physicians, according to Verispan, a health-care market-research firm in Pennsylvania. The drug industry argues, with reason, that gift giving evolved as a necessary tool for sharing information about new drugs with busy physicians who needed incentives to stop and listen."

According to Dr Gulhati, Editor of *MIMS India*, companies routinely spend on "educational" seminars: "lavish but misleading events based on selective quotes from selected articles and inevitably such events are followed by lavish meals laced with alcohol… Some years back German Remedies held such so-called educational seminars all over India where the virtues of anti-hypertensive clonidine were explained in great detail. Within a month, another division of the same company held another seminar where another anti-hypertensive Xipamid was placed at the top while clonidine was at Number 10 the bottom!"[10] In India, medical association journals lend themselves to include special advertisement supplements, which in effect turn out to be a marketing outlet for a particular drug or class of drugs of a drug company. However in India advertisement in journals is a relatively low source of influence and persuasion compared to gifting and related inducements and of course part or full sponsorship of seminar events and the creation and

1.1 Doctors as KOLs: "Magic Realists" of the Medical World

Key Opinion Leaders (KOLs) are influential specialists in their fields such as doctors at teaching hospitals, senior consultants, authors, etc. An endorsement by a KOL in favour of new products or new uses of old products is a top priority for pharma companies. Aggressive, often highly unethical, tools are employed to capture KOLs. Consider the following actions of drug companies and their KOLs:[11]

- Sun Pharmaceuticals sponsored over a dozen "educational seminars" all over India to advocate Letrozole's use in infertile young women. KOLs were paid up to Rs 30,000 per lecture to endorse the new indication. It is illegal to promote any drug for unapproved indications.[12]
- According to one "Key Opinion Leader" of Jammu, he has already prescribed cisapride to 40,000 patients. Furthermore, he prescribes cisapride to 150 patients every week. Another KOL from Jammu says the same thing in the same language and he too has prescribed for 40,000 patients and from 1990 at that when the drug was not even marketed! Another KOL says it is okay to give it to infants for pain in abdomen when it is prohibited for use in children and yet another has determined that the side-effects of cisapride are to be found in 0.0001 % of the patients whereas the USFDA says it is about 5 percent! With such KOLs as doctors who needs enemies!
- Most Indian medical journals would have non-specific vague quotes from doctors testifying to the supposed efficacy of a drug.
- In return, professional associations endorse products: for instance, the Delhi branch of the Indian Medical Association endorsed nimesulide and in its so-called survey for the purpose, the sample of adults to children taken if extrapolated results in the number of children of India being more than the population of India![13]

- The *Journal of Indian Medical Association* (*JIMA*) has a "Research Analysis Section" that in effect provides a platform to Pharma companies to market their products. Example: *JIMA* (Volume 99, No 3, July-Sep 2001) published two articles in a span of a few months both promoting iron polymaltose (IP) preparations claiming superiority of IP over ferrous fumerate and then quotes the publication of these papers in marketing Mumfer, its brand of IP!

1.2 Cozy Connections with Professional Associations

We look at some instances of the cozy connections between professional associations and the drug industry. Patients may be alarmed that their prescribers, with a few honourable exceptions, can get swayed so easily. Drug companies sponsor conferences and here are some examples:[14]

- The Indian Medical Association requested major drug companies to become "Principal Sponsor" of its All India Conference by paying a whopping Rs. 75 lacs. The Company could also become "Full Day Sponsor" by paying Rs. 25 lacs. Funds were sought to feed the participants at the rate of Rs. 10 lacs for each lunch and Rs. 15 lacs for the banquet.

- Indian College of Interventional Cardiology asked for Rs. 5 lacs for placing a banner in the main hall.

- Indian Society of Critical Care Medicine sought Rs. 15 lacs for "Principal Sponsor", Rs. 5 lacs for each lunch and Rs. 10 lacs for banquet.

- The Maharashtra Branch of the Indian Society of Anaesthesiologists sought Rs. 500,000 to designate a company as the "Main Sponsor of the Conference."

- The Indian Orthopaedic Association asked Rs. 10 lacs from a company towards "Sponsorship of the Main Hall" whatever it means. For each meal the companies were asked to pay Rs. 8 lacs.

- National College of Chest Physicians/Indian Chest Society sought Rs. 15 lacs for three lunches and 17 lacs for two dinners for its conference in Ahmedabad.

- Indian Association of Surgical Oncology wanted Rs. 4 lacs from any company that wanted to become "Principal Sponsor."

- Indian Association for Cardiovascular-Thoracic Surgeons sought Rs. 1 lac to give an opportunity to any company to introduce its product in 7 minutes.

- Indian Clinical Epidemiological Network that held a conference in Agra sought Rs. 1,00,000 to take participants from Delhi to Agra "for augmenting Quality of Hospitality." Another Rs. 1,00,000 were sought to serve "A Glass of Beer/Wine during Dinners and Banquets."

- Three companies namely Organon (India) Ltd, Indo-French Marketing Company and Universal Biomedics were the principal financiers of National Association of Sexology Conference.

- Top British cardiologists can collect more than $8,700, for an hour of lecturing to colleagues, and they also may be paid for putting their names to articles that review drugs in medical journals, according to a report by members of the British House of Commons in April 2005.[15]

- There is always a "close bondage between the medical profession and pharmaceutical industries" wrote the Organising Secretary of the Cardiological Society of India seeking funds from the drug companies.

- "Financial support from industries is mandatory to make Annual Conference of Cardiovascular-Thoracic Surgeons successful" - Organizing Secretary.

- "The sponsorship of the Clock Room will be Rs. 1 lac while balloons will cost Rs. 1 lac each." -- Organising Secretary, National Conference on Pulmonary Diseases.

- "An article on a product of interest to your Company in the Souvenir can be published on payment of Rs. 1 lac." - Editor, Souvenir of All India Medical Conference.

How Drug Industry Influences Doctor's Prescriptions

…The temptations offered by the drug industry are too irresistible to be turned a blind eye to. Doctors, however, argue that they are not gullible enough to be influenced by glib talks and gifts. Unfortunately this is a self-illusion. The Forum for Medical Ethics, Mumbai, in its recent survey asked doctors if going on a drug company sponsored cruise would affect their prescriptions towards the company's products, the overwhelming said No. But most said yes, when asked if a sponsored cruise influenced the prescription practice of at least one doctor they knew. Indeed doctors who frequently see drug representatives are more willing to prescribe new drugs, are more likely to write a drug that is clinically not indicated, and do not like ending consultations with advice only. After attending sponsored conferences, irrational prescriptions start flowing from their pens. And the cosy relationship between doctors and medical representatives does not escape patients' discerning eyes.

As Dr. Anand aptly puts it, "No one should have any doubt that the costs of industry sponsored trips, meals, gifts, conferences and symposia are simply added to the prices of drugs and devices. Drug industry treats doctors as prescribers and not cares givers. When we attend a sponsored banquet, we may be adding significantly to the drug prices in India."

Reproduced by kind permission of J. Collier. Quoted in WHO EDM, Issue No. 31, 2002

"Doctors everywhere love freebies"

Dr. M. K. Mani wrote of one conference, "We can easily afford to buy an odd pen or briefcase, a flask or a shopping bag. Yet no sooner did some company announce on the very loud audio system that there were some goodies available at some stall, a long queue would form there leaving the speaker to cast his wisdom on empty chairs. Do we need to demean ourselves to this extent? Should we allow commercial interests to dominate us so completely?" Richard Smith reinforces this further, "That healthcare professionals can be bought for a self adhesive memo pad, pen, coffee mug, or pizza is pathetic. Are we so poor that we cannot buy our own pen, note pad or lunch?"

Source: Kalantri, S.P. "Drug Industry and Medical Conferences", *Indian J. Anaesth. 2004*; 48 (1): 28-30. References cited in the original.

2. Clinical Trials, Research Publications and Conflicts of Interest

2.1 "Regulatory Capture": India, a Soft Target for Clinical Trials

We give in Annexure 1 a brief primer on what is a clinical trial.

Given below are some scams involving drug trials in India and that happened between the period 1999-2005:[16]

- *Unethical Trials in Collaboration with John Hopkins Scientist*: New chemical entities called M4N or tetra-O-methyl nordihydroguaiaretic acid and G4N or tetraglycinyl nor-dihydro-guaiaretic acid, discovered in the United States, were unlawfully tested on 26 oral cancer patients at the Regional Cancer Centre (RCC) at Thiruvananthapuram, Kerala, between November 1999 and February 2000. Under unrelenting pressure from the media and NGOs, an unwilling Government was literally dragged to take action. Instead of penalizing the guilty, further research on M4N and G4N was merely suspended for six months! In such cases, the law provides for three months imprisonment for the guilty.[17] Soon after it was tested on 36 mice in the US. The trial of another drug, Foscan, at the RCC has raised hackles as the Food and Drug Administration (FDA) of the US and the European committee empowered to give approval for drugs have more than once blocked clearance. A senior RCC doctor said the issue came to light "when one of the doctors in RCC found out that his patients were being used as guinea pigs for this new derivative, without his consent." "When he protested he was sidelined and he has now approached the State Human Rights Commission and the Kerala High Court for justice." "The team led by the RCC director Dr M. Krishnan Nair instead of removing the tumors on the 24 patients as soon as they were detected, delayed the surgical intervention for varying periods to find out the efficacy of the chemical on cancer cells," he said. In fact, Nair, in a press statement took a joint credit with John Hopkins University in announcing that the drug had been effective in treating certain cancers caused by viruses, the media reports have said. Even as we go to the press, *Frontline* reported:[18]

  > More than four years after a petition seeking compensation was filed before the Kerala Human Rights Commission (HRC) by one of the 27 patients involved in the controversial Hopkins-RCC drug trials, a Division Bench of the Kerala High Court quashed it on November 17, accepting technical objections raised by the Regional Cancer Centre (RCC) and its former Director, Dr. M. Krishnan Nair. They pleaded that as per the Protection of Human Rights Act, the complaint ought to have been filed within one year of occurrence of the event for it to be considered by the Commission. The patient M. Gopalan, therefore, lost his case purely on legal technicalities, with the commission never looking into his complaint of serious ethical violations by the doctors who experimented on him without his voluntary or informed consent.
  >
  > The HRC had initially rejected the RCC's and Dr. Krishnan Nair's objections. So had a single-Judge Bench of the High Court subsequently. (Another petition filed by Dr. V. N. Bhattathiri is pending before the Commission.)
  >
  > Gopalan, then a patient awaiting surgery at the RCC, received the last in a series of controversial injections in mid-January 2000. The Division Bench accepted the argument that Gopalan should have filed the complaint within a year of the date of that injection. Perhaps it does not matter any more. Gopalan died a year after filing the complaint.

- Cilansetron, a new molecule of Solvay Pharmaceuticals not approved anywhere in the world was cleared for Phase III trials even though only Phase II trials had been conducted abroad.

- Cilostazol, a product of Otsuka, was cleared by DCGI based on incomplete, inadequate information on adverse effects. Common serious side-effects such as angina and myocardial infarction were not even mentioned. Needless to say such omissions can be life-threatening in study subjects.

- The protocol of the drug Tacrolimus submitted by Panacea Biotec and cleared by DCGI was not only vague but deficient and defective beyond imagination. It did not even state the Phase of the trial, an elementary requirement, and omitted all important serious adverse effects such as malignancies, cardiomyopathy, lymphoproliferative disorders, etc.

- It appears that some protocols and accompanying documents such as Investigator's Brochures are not even read by DCGI. Otherwise how does one explain approval of patently defective clinical trials? This perception is strengthened by the super speed with which some proposals are cleared: a voluminous protocol on trastuzumab sponsored by Roche was approved within 5 working days. It is humanly not possible to read and analyze the bulky documents in such a short period.

- At least three patients in Hyderabad being tested for the efficacy and safety of recombinant streptokinase have died. Without any independent enquiry, Shantha Biotech that sponsored the trial washed off its hands by labeling the death of "trial subjects", as they are impersonally called, to "causes other that the use" of the drug! Independent sources placed the death toll at eight.

- Dharmesh Vasava, a 22-year-old "volunteer" from Bharuch in Gujarat had died while participating in tests on citalopram sponsored by Sun Pharmaceuticals. According to another participant of the same trial, the subjects were lured with money by agents working for the Company. Such exploitative inducements are both unethical and illegal.

- Erythromycin was inserted into the uteri of 790 poor, illiterate, unsuspecting women in rural West Bengal by two self-styled researchers to test its contraceptive effect without government approval and consent from participants.

- A human trial on Zoniporide, an American new drug, was approved without adequate and mandatory cancer and reproductive studies on animals.

"It may sound incredible but animals subjected to experiments in America enjoy more protection than humans in India. A trial done on an animal without approval from the relevant authorities is fined Rs. 110,000 (US$ 2,500) under Animal Welfare Act. In India, more than 1,200 young women have been treated worse than animals," says Dr Gulhati in *MIMS India*.[19]

> Most drug trials in India are conducted without any arrangement for compensation in case of study-related injury disability or even death in human subjects in violation of Indian Council of Medical Research (ICMR) Guidelines.
>
> The investigators for clinical trials are chosen by sponsoring commercial companies. Some such investigators are, or have been, beneficiaries of largesse from the pharmaceutical manufacturers

> including expensive gifts and air tickets for travels abroad. Neither the regulatory authorities nor the Hospital Ethics Committees seek information from investigators about their financial relationship with drug manufacturers.

Many other instances may be given of well-known companies in India and abroad whose products have failed and continue to fail routinely. As India becomes a "destination" for clinical trials, it is the ordinary person who is at risk, in the absence of information in the public domain of clinical trials being conducted. Indeed a new type of colonialism is in the offing as more Indians are being readied as guinea pigs, and as usual some of India's own elite act as instruments of this colonialism. More importantly, the Drug Controller General of India often does a balancing act between public health interests and making Indian industry "world class" and competitive goals which could be complementary but in the context of the irrationalities and distortions in the market, it appears to be loaded in the favour of drug industry than people at large. How can we have a "world class" drug industry if the country's chief drug regulatory agency does not apply the highest standards of bioethics in clinical trials - to cite just one area for instance?

Apparently this is true of the US FDA also. Dr David Graham, Associate Director for Science and Medicine in the FDA's Office of Drug Safety, gave relevant evidence to the US Senate Committee on Finance in hearings following the withdrawal of Vioxx and subsequently spoke about the relationship between regulators and industry:[20]

> The FDA has become an agent of industry. I have been to many, many internal meetings and, as soon as a company says it is not going to do something, the FDA backs down. The way it talks about industry is 'our colleagues in industry'… it is rather because the body is entirely geared towards concentrating on approving drugs, doing little once they are on the market ...

And further added:

> The organizational structure within CDER (Center for Drug Evaluation and Research) is entirely geared towards the review and approval of new drugs. When a CDER new drug reviewing division approves a new drug, it is also saying the drug is "safe and effective." When a serious safety issue arises post-marketing, their immediate reaction is almost always one of denial, rejection and heat. They approved the drug so there can't possibly be anything wrong with it. The same group that approved the drug is also responsible for taking regulatory action against it post-marketing. This is an inherent conflict of interest. At the same time, the Office of Drug Safety has no regulatory power and must first convince the new drug reviewing division that a problem exists before anything beneficial to the public can be done. Often, the new drug reviewing division is the single greatest obstacle to effectively protecting the public against drug safety risks. A close second in my opinion, is an ODS management that sees its mission as pleasing the Office of New Drugs.
>
> The corporate culture within CDER is also a barrier to effectively protecting the American people from unnecessary harm due to prescription and OTC drugs. The culture is dominated by a world-view that believes only randomized clinical trials provide useful and actionable information and that postmarketing safety is an afterthought. This culture also views the pharmaceutical industry it is supposed to regulate as its client, over-values the benefits of the drugs it approves and seriously under-values, disregards and disrespects drug safety.

2.2 Clinical Trials and "Tainted Evidence"

Some editors of reputed medical journals[21] have been convinced for sometime now that medical journals are the marketing arm of pharmaceutical companies. In a joint statement titled, "Sponsorship, Authorship, and Accountability" in September 2001, 13 of the world's leading medical journals accused drug companies of distorting the results of scientific research for the sake of profits. *The Lancet, the New England Journal of Medicine, the Journal of the American Medical Association* and other major journals accused the drug giants of using their money - or the threat of its removal - to tie up academic researchers with legal contracts so that they are unable to report freely and fairly on the results of drug trials."We are concerned that the current intellectual environment in which some clinical research is conceived, study subjects are recruited, and the data analyzed and reported (or not reported) may threaten this precious objectivity."[22]

Scientists, often from cash-starved university departments, noted the statement, may be prevented from having access to the raw data gathered in the trial which would tell them how well or not the drug worked and whether there were side-effects. They may be given no say in the way the trial is designed and they may have only limited participation in interpreting the results. "These terms are draconian for self-respecting scientists, but many have accepted them because they know that if they do not, the sponsor will find someone else who will. And, unfortunately, even when an investigator has had substantial input into trial design and data interpretation, the results of the finished trial may be buried rather than published if they are unfavourable to the sponsor's product," said the commentary which ran in 12 of the 13 journals.

According to Richard Horton, editor of *The Lancet*, and one of the signatories, "The patient should know who is in control of the study. Are you - my doctor or the scientist doing the study - in control or is the pharmaceutical company in control? They are never told anything of the sort. At the moment, informed patient consent is a fabrication."[23]

Academic scientists had little choice but to accept the restrictions imposed on them, the statement went on to note, because they knew that otherwise the funding they needed for research would go to the increasing number of private contract research organizations (CROs). These organizations in the USA received up to 60% of the research grants handed out by pharmaceutical companies in recent years.

> As CROs and academic medical centers compete head to head for the opportunity to enroll patients in clinical trials, corporate sponsors have been able to dictate the terms of participation in the trial, terms that are not always in the best interests of academic investigators, the study participants, or the advancement of science generally.

The editors decided to take action, henceforth, by requiring all authors to disclose details of their own and the sponsoring pharmaceutical company's roles in the study. Some editors would be asking for a signed declaration from the author that they accept responsibility for the trial. If the company has sole control of the data, the journals will not publish the study.

> … contracts should give the researchers a substantial say in trial design, access to the raw data, responsibility for data analysis and interpretation, and the right to publish, the hallmarks of scholarly independence and, ultimately, academic freedom. By enforcing adherence to these revised requirements, we can as editors assure our readers that the authors of an article have had a meaningful and truly independent role in the study that bears their names. The authors can then stand behind the published results, and so can we.[24]

Elsewhere Richard Horton, editor of the *The Lancet*, wrote that "journals have devolved into information-laundering operations for the pharmaceutical industry."[25] Advertisements, however, are the least form of corrupting influence according to Richard Smith,[26] the former editor of *British Medical Journal (BMJ)*. It has more to do with sponsored clinical trials and the reporting of clinical trials seen by the public at large as a neutral form of evidence. "Readers see randomised controlled trials as one of the highest forms of evidence. A large trial published in a major journal has the journal's stamp of approval (unlike the advertising), will be distributed around the world, and may well receive global media coverage, particularly if promoted simultaneously by press releases from both the journal and the expensive public-relations firm hired by the pharmaceutical company that sponsored the trial. For a drug company, a favourable trial is worth thousands of pages of advertising, which is why a company will sometimes spend upwards of a million dollars on reprints of the trial for worldwide distribution. The doctors receiving the reprints may not read them, but they will be impressed by the name of the journal from which they come. The quality of the journal will bless the quality of the drug." (See also box below on *Examples of Methods for Pharmaceutical Companies to get the Results they want from Clinical Trials*). And Smith continues:

> Fortunately from the point of view of the companies funding these trials -- but unfortunately for the credibility of the journals who publish them -- these trials rarely produce results that are unfavourable to the companies' products. Paula Rochon and others examined in 1994 all the trials funded by manufacturers of nonsteroidal anti-inflammatory drugs for arthritis that they could find.[27] They found 56 trials, and not one of the published trials presented results that were unfavourable to the company that sponsored the trial. Every trial showed the company's drug to be as good as or better than the comparison treatment.

For yet another instance in this vein, see the box below, *Aspirin Dispute is Fueled by Funds of Industry Rivals*.

2.3 Need for Clinical Registry

We have already mentioned above how India has become a destination for "regulatory capture", a soft target for clinical trials by CROs (Contract Research Organisations) and drug researchers, producing at best what could be termed as biased research emanating from tainted evidence and violating human rights of poor patients in the worst possible way. If anything this indicates a need for a clinical trial registry in the public domain and India's regulatory authorities may well wake up now than later. In the United States, the Food and Drug Administration Modernization Act requires that all trials on life-threatening diseases be registered into <http:/ClinicalTrials.gov>, a register maintained by the National Institutes of Health, yet only 48% of industry-sponsored trials were registered during the initial period of the law's implementation.[28] Selective reporting of results to benefit drug company interests rather than public health seems to be happening: In 2004, GlaxoSmithKline settled a US$2.5 million lawsuit for suppressing trial results showing that its antidepressant paroxetine (Paxil) increased suicidal ideation in children. As part of the settlement, GSK agreed to set up a public register of all clinical trials on all of its drugs.[29] This is contrary to a longstanding understanding, and one supported by regulatory agencies world over, that clinical trial results are company property and commercially confidential. IP and WTO need not come in the way of transparency the whole point of IP, at least the way drug industry has advocated it, is to let everybody see what you are doing.

Again more recently, Merck and Pfizer have been criticized for withholding results showing increased risk of heart disease from COX-2 drugs such as rofecoxib (brand name Vioxx), which was withdrawn from the market because of these risks.[30]

Aspirin Dispute is Fueled by Funds of Industry Rivals

Over the past four years, medical publications have become full of talk about "aspirin resistance" -- suggesting that millions who take an aspirin a day to prevent heart attacks are wasting their effort. If that is true, widespread testing might be needed to detect the condition and doctors might have to turn to aspirin substitutes costing $4 a day.

But reports and commentary on the subject often fail to point out that many of those raising alarms about aspirin resistance have financial ties with drug and test makers who stand to profit from the idea's acceptance ...

Last July, Harvard Medical School associate professor Daniel Simon warned that aspirin resistance may afflict as many as 30% of the 25 million Americans taking aspirin for their hearts. He wrote in *Physician's Weekly*, a trade publication, that these people are at higher risk for heart attacks and strokes and may need other anticlotting drugs.

The article didn't mention that Dr. Simon receives research funding from Accumetrics Inc., a privately held San Diego company that makes a test to measure aspirin resistance, and from pharmaceuticals maker Schering-Plough Corp., which sells a drug being tested as a potential benefit for patients deemed aspirin-resistant. He is also a consultant and paid speaker for Schering-Plough. *Physician's Weekly* Managing Editor Keith D'Oria says he knew of the ties, but didn't disclose them. He said the publication never discloses possible conflicts and instead uses the information for other purposes, such as contacting drug companies listed by doctors to see if they might place an ad near the doctor's commentary.

The issue of aspirin resistance is a powerful example of how key academic researchers with a financial interest can influence the care Americans receive. Fears of aspirin resistance have boosted sales of the anticlotting pill Plavix, the world's second best-selling drug after cholesterol fighter Lipitor. Even some doctors who are trying to debunk aspirin resistance have financial ties -- to aspirin maker Bayer AG.

"There is a real issue of who you can get unbiased opinion from in medicine," says John Eikelboom, a hematologist at McMaster University in Hamilton, Ontario, who has consulted for both an aspirin manufacturer and the maker of an alternative blood-thinner. "It is a terrible problem ... I try to be honest with myself, but I can't pretend I will always be as honest as necessary."

By David Armstrong, *Wall Street Journal,* April 24, 2006 (copied as fair use)

A humourous portrayal of a drug representative's visit to a doctor, but the Australian Code of Conduct sets standards for the country's pharmaceutical representatives.

Examples of Methods for Pharmaceutical Companies to get the Results they want from Clinical Trials

Conduct a trial of your drug against a treatment known to be inferior.

Trial your drugs against too low a dose of a competitor drug.

Conduct a trial of your drug against too high a dose of a competitor drug (making your drug seem less toxic.)

Conduct trials that are too small to show differences from competitor drugs.

Use multiple endpoints in the trial and select for publication those that give favourable results.

Do multicentre trials and select for publication results from centres that are favourable.

Conduct subgroup analyses and select for publication those that are favourable.

Present results that are most likely to impress: for example, reduction in relative rather than absolute risk.

Source: Richard Smith. "Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies." PLoS Medicine, *Vol 2, Issue 5, May 2005 and at <http://medicine.plosjournals.org>. Smith is a former* editor of BMJ

Drug companies, driven by economic pressures, conduct often post-approval studies.[31] Merck and Pharmacia did extensive post-approval studies to show that their arthritis pain medications, Vioxx and Celebrex, were easier on the stomach than older, cheaper painkillers. Merck's study, involving more than 8,000 adults, showed Vioxx causes fewer stomach complications than the painkiller naproxen, but also found it increases the risk of heart attacks. Both facts were widely reported in medical journals and the media, and the company stepped up promotion of the drug's safety since the FDA added that information to the drug's label. Finally Merck's Vioxx was taken off because of the fortuitous results of an efficacy study not a safety study (see box below "It is better to kill a drug than kill a patient".)

"It is better to kill a drug than kill a patient"

… More importantly, there were no attempts to design and carry out large safety studies to prove or disprove the link of Vioxx to heart attacks. Apparently, a 30,000 patient study had been announced in November 2001 but never started. Last week, *New York Times* reported that Merck had considered a cardiovascular outcome study, but decided that it would send the "wrong" marketing and public relations signal. "At present, there is no compelling marketing need for such a study," said a slide prepared for a meeting of senior executives." Data would not be available during the critical period. The implied message is not favorable." It is regrettable that scientific decisions on patient safety are influenced by perceived marketing and public relations concerns. In my opinion, it is better to kill a drug than kill a patient.

It is important to note that the APPROVe study which conclusively proved the increased risk of Vioxx was not a safety study it was an efficacy study, designed to add another indication for Vioxx treatment. It was not large enough to detect a heart attack risk that it did find a risk was a lucky break for patients, but this is not what it was designed to do.

The failure to conduct large long-term safety studies subjected millions of patients over 4 years to a drug whose safety had been questioned by the FDA even before its approval. This is not the proudest chapter in drug approval in the US …

- Gurkirpal Singh, MD, affidavit before US Senate reviewing the science of Cox-2 inhibitors and the link of rofecoxib to heart attacks[32]

Pfizer tried hard to continue marketing its block buster Lipitor (see also box below, *Pfizer Fraud Alleged*). Likewise, Pharmacia circulated preliminary results suggesting that its study of more than 8,000 patients showed that Celebrex was easier on the stomach than ibuprofen. But, in the end, the FDA ruled that the study showed no such benefit and the *British Medical Journal* criticized the company for "distributing overoptimistic short term data" from its study.

Pfizer Fraud Alleged

Pfizer misled consumers into using its anti-cholesterol drug Lipitor despite the absence of evidence from clinical trials that the drug or others in its class are of any benefit to large segments of the population, according to a consumer class action lawsuit filed against the world's largest drug maker in October.

According to Steve Berman, the lead attorney for the proposed class, Pfizer promoted Lipitor by claiming it prevents heart disease in women and the elderly, even though no clinical test has established such a benefit.

The lawsuit alleges that Pfizer engaged in a massive campaign to convince both doctors and patients that Lipitor is a beneficial treatment for nearly everyone with elevated cholesterol, even though no studies have shown it to be effective for women and those over 65 years of age who do not already have heart disease or diabetes.

Lipitor is in the class of cholesterol-lowering drugs called statins and it is the best-selling drug in the world, with sales in 2004 of more than $10 billion. "The idea that lowering cholesterol always reduces the risk of heart disease has become the conventional wisdom, which drug companies like Pfizer have taken great pains to promote," says Dr. John Abramson, clinical instructor of ambulatory care at Harvard Medical School and author of Overdosed America: The Broken Promise of American Medicine. "But for women under 65 and people over 65 with no history of heart disease or diabetes, the evidence just isn't there. Millions of women and seniors are spending huge sums to take Lipitor every day despite a lack of proof that it's doing anything beneficial for them, and may actually be harming the elderly."

Source: <http://www.multinationalmonitor.org/mm2005/092005/names.html>

Elsewhere, it has been reported that, "Five out of six systematic reviews published in the last two years have shown that research that is sponsored by a drug manufacturer is more likely to yield a positive result for the company's product than research that is independently sponsored."[33]

These studies are hardly supervised either by the FDA in USA or by the companies themselves. The studies themselves are not risk free and side effects come to light only when a drug is used widely. Doctors who test post-approval drugs are more likely to prescribe them to their patients. Post-approval studies are thus no more than a marketing tool.

Consider the following witness given to the House of Commons Report on *The Influence of the Pharmaceutical Industry*, 2004-05:[34]

> In order for a drug to be licensed it has to show that it is more effective than a placebo, usually in two controlled trials. However, according to Prof Healy, companies can run 10 or more trials in carefully selected samples using instruments designed to pick up any effect and, even if the results show that the drug failed to beat placebo in the majority of trials, the drug may still be licensed. The trials producing negative results are commonly identified as failed trials rather than drug failures. Whether the experimental drug is compared to placebo or a comparator drug will affect the outcome. Common flaws in trial design include the use of inappropriate comparator drugs, such as those associated with a higher risk of side-effects than others in the therapeutic group. Selection of dosage may also be used to skew results. Administration of a comparator drug in unduly low doses may result in reduced levels of efficacy. Administration of the comparator drug at relatively high dosages might make the test drug appear safer than it really is. These and other methods of trial

design may show the new drug in a misleadingly positive light.

Also of concern, because it may lead to an over-estimate of the drug benefit, is reliance on surrogate markers of efficacy or disease (in one case, higher numbers of extra abnormal heartbeats were assumed to correlate with increased risk of death). However, such markers may not be directly relevant to treatment outcomes (in this case, drugs used to reduce the number of heartbeats were actually associated with increased mortality). The use of combined clinical outcomes can also be problematic; making it difficult to assess which end point has really changed, while the use of inappropriate safety markers makes extrapolation to safety in clinical practice even harder. *Cancer Research UK* criticised the industry for not investigating the wider effects of drugs and focusing on specific outcomes.

Several witnesses were also concerned about the duplication of research. Some organisations make considerable efforts to avoid this problem: the MRC requires groups seeking financial support to identify existing evidence before applying, to show that the new research builds on previous lines of investigation. On the other hand, others either did not attempt to find out about previous research or could not get access to it. Sir Iain Chalmers argued that a systematic review of existing evidence prior to the planning and reporting of new clinical trials should be mandatory. The following example shows what can happen if such a review is not undertaken:

After reviewing the experience of thousands of patients who had participated in controlled trials of new calcium-blocking drugs given to people experiencing a stroke, a Dutch team found no evidence to support the increasing use of these drugs in practice, or for the large numbers of clinical trials that had been performed … Furthermore, when they subsequently prepared a systematic review of the relevant animal studies they found that these had never suggested that the drug would be useful in humans.

2.4 Disease Mongering: "Corporate Construction of Disease"*

One of the important ways drug companies make money is by telling people they are sick, even when they are passing through one of life's many normal transitions. This "disease-mongering" suits the medical profession too, as it helps in medicalising problems. Some examples:

- In India, piractecam is being promoted for vague conditions like "intellectual decay," "social maladjustment," "lack of alertness," "changes of mood," "deterioration in behaviour" and "learning disabilities in children associated with the written word." The recommended duration of treatment for the last indication is "entire school year" in dose of "3g per day" i.e. 7-8 capsules of 400mg daily. If the drug is administered for the entire school year as recommended, it will mean parents buying at lease 2,700 capsules at a cost of Rs. 12,775 year after year. The unending claims of the drug's efficacy include the treatment of sickle cell anaemia, stroke and vertigo. In Britain, piracetam (Nootropil) is permitted for use in just a single indication, a rare disorder called cortical myoclonus, that too only as an adjunctive therapy (Reference: Britain National Formulary). While in India, the drug is being promoted for use in young children, in Britain its use is contraindicated for adolescents under the age of 16 years. "If the Indian company marketing piracetam is to be believed, the drug is nothing short of nectar.

*For more on the phenomena of disease mongering, see the papers at *PLOS Medicine*, April 2006, <http://collections.plos.org/diseasemongering-2006.php>.

It has no contraindications, no need to observe any precautions, no interactions and no adverse drug reactions. In Britain, the drug is contraindicated in hepatic and renal impairment, during pregnancy and lactation. It is to be used cautiously in elderly. Its side-effects include: diarrhea, weight gain, insomnia, nervousness, depression, hyperkinesias and rash. It can interact with warfarin and result in bleeding. Piracetam is not marketed in the United States."[35]

- Buclizine (brand Longifene in India) is being promoted as appetite stimulant while the drug itself is not commercially available in the US and is restricted worldwide for treatment of migraine in combination with analgesics. Internationally reported adverse effects include: drowsiness, blurred vision, diarrhea, difficulty in passing urine, dizziness, dryness of mouth, tachycardia, headache, nervousness, restlessness, hallucinations, skin rash and upset stomach. Bottles of Longifene, the only brand of buclizine being sold in India do not contain either the package insert or the patient information leaflet.[36]

- Ever since Hepatitis B vaccination started being made by Indian companies starting with Shanta Biotech of Hyderabad, the classes of people who "need" Hepatitis vaccine compulsorily has been expanding; the Ministry of Health and Family Welfare (MOHFW) would have us believe that it is a bigger problem than AIDS (so is iron deficiency anemia). And suddenly India has had a glut of Hepatitis B vaccine manufacturers all in search of a market. Some of them were/are even on the verge of closing. They have all succeeded in convincing policy makers that hepatitis B vaccine need to be given to all newborns by including it in the National Immunization Programme. Business media have gleefully reported this as a "shot in the arm" for the ailing vaccine industry.[37]

- Warner Lambert invented a condition called "halitosis" which makes ordinary bad smell in the breath sound serious. Sales of Listerine rose from US $100,000 to US $4 million in six years.[38]

- In the 1980s Glaxo needed to expand their market for ranitidine (brand Zantac). They again created a condition called "gastro-oesophageal reflux disease (GERD)" which is a serious sounding name for heartburn, an age-old complaint. The company also set up a platform called the Glaxo Institute for Digestive Health, which in due course led to a PR exercise called Heartburn Across America. Annual sales of Zantac peaked at US $ 2 billion.

- *"Capturing impotence in an acronym"*: During the 1990s Pfizer had to create a market for sildenafil citrate ("Viagra") and it ended up calling the broader condition of impotence as "erectile dysfunction" (ED). Calling impotence ED caused probably less embarrassment to shy patients as they could now discuss a medical problem called ED with their doctors!

- Manufacturers of fluoxetine (a serotonin re-uptake inhibitor) marketed in the name of "premenstrual dysphoric disorder," a different name for a severe form of premenstrual syndrome, a routine hormonal transition. Again here the marketing strategy was to frame the "disease prevalence to maximize the size of the medical problem." Pfizer even setup an organization called Impotence Australia that would host the advertisements in the media. In the US, Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants have been widely promoted through what is called Direct-to-Consumer Advertising (DTCA). In a paper published in *PLoS Medicine*, Jeffrey R. Lacasse, Jonathan Leo observe:[39] "The impact of the widespread promotion of the serotonin hypothesis[40] should not be underestimated. Antidepressant advertisements are ubiquitous in American media, and there is emerging evidence that

these advertisements have the potential to confound the doctor-patient relationship." A recent study by Kravitz et al.[41] found that pseudopatients (actors who were trained to behave as patients) presenting with symptoms of adjustment disorder (a condition for which antidepressants are not usually prescribed) were frequently prescribed paroxetine (Paxil) by their physicians if they inquired specifically about Paxil. In 1998, at the dawn of consumer advertising of SSRIs, Professor Emeritus of Neuroscience, Elliot Valenstein, summarized the scientific data by concluding, "What physicians and the public are reading about mental illness is by no means a neutral reflection of all the information that is available."[42] The current state of affairs has only confirmed the veracity of this conclusion. The incongruence between the scientific literature and the claims made in FDA-regulated SSRI advertisements is remarkable, and possibly unparalleled."[43]

- "A legendary example of this condition (called) branding strategy was the development of Xanax (alprazolam) for panic disorder in the 1970s. In DSM-II, panic disorder fell under the broad category of anxiety neurosis. Without a well-branded condition, patients experiencing panic attacks often went to cardiologists, thinking their problem was a heart condition, only to be labeled "cardiac complainers" and hypochondriacs due to a lack of physical pathology. Dr. David Sheehan, a pioneering thought leader in the field of panic, helped characterize the condition and push for a new way to diagnose and treat it. Upjohn, the makers of Xanax, helped fund this early research, as well as publications and speaking tours to cardiologists to help raise awareness of the heart-brain connection in the minds of panic disorder patients. Xanax was the only benzodiazepine to be studied that showed clear evidence of effectiveness. Through an unrestricted grant to the National Institute of Mental Health, a three-day thought leader conference resulted in a published consensus on the diagnostic criteria of panic disorder and how best to treat it. Xanax was the first to receive an exclusive indication, thereby maintaining its leadership in anxiety disorders. Since the release of DSM-III in 1980, which first recognized panic disorder as a distinct condition, its incidence has grown 1,000-fold, and newer antidepressants have stepped in to foster expanding ideas about panic."[44]

- In Australia, baldness in men was medicalised by Merck to sell its hair-growth drug finasteride (Propecia); Merck funded a new International Hair Study Institute so that men can wise up to the bald truth by consulting their doctors. Hair loss, the public was told, could lead to panic and other emotional difficulties and even have an impact on job and well-being! Needless to say there were several articles around 1998-2002 in the media about the life-threatening process called hair loss.[45]

- Irritable bowel syndrome (IBS), a common functional disorder, found a drug in GSK's Lotronex (alosetron hydrochloride) and GSK used a "medical education" firm In Vivo to "shape" medical and public opinion a plan that included setting up an "Advisory Board", consisting of preselected KOLs (Key Opinion Leaders) in each Australian state the campaign was stopped because the US FDA recommended withdrawal of the drug after reports of serious and sometimes fatal adverse reactions. FDA investigators[46] discovered that the use of Lotronex could result in ischemic colitis, a potentially life threatening condition which is caused by reduced blood flow to the colon. Additionally, the drug can cause severe constipation, which can result in a ruptured bowel. As of October 2000 there had been 91 incidences of hospitalization (many more likely went unreported) in which some patients required surgery and at least five died. As a result, GlaxoSmithKline agreed to remove the drug from the market in November 2000. However, in June 2002, the USFDA, facing pressure from desperate patients, announced June 7, 2002 the approval of a supplemental New Drug Application (sNDA) that allows

restricted marketing of Lotronex (alosetron hydrochloride), to treat only women with severe diarrhea-predominant irritable bowel syndrome (IBS).

- In 1997, Roche started promoting its antidepressant Aurorix (moclobemide) as a valuable treatment for "social phobia." Its PR company issued a press release saying more than one million Australians had a "soul-destroying condition" called social phobia. Soon Roche's promotion of Aurorix became case-study material of positive action in marketing circles even as the medicalisation of human misery was pushed further.

2.5 Pharma Ghost Writers

One could understand if marketing was confined to inventing unwarranted uses of medicines: it could be blamed on pin-striped MBAs. But we have seen research trials are illegally conducted in India with poor regulatory oversight, and it is difficult to know who is doing what clinical trial at any given time. A further and more blatantly unethical form of manufacturing "consent" is by ghostwriting research papers. Dr Richard Smith, editor of the *British Journal of Medicine*, admitted ghostwriting was a 'very big problem'. "We are being hoodwinked by the drug companies. The articles come in with doctors' names on them and we often find some of them have little or no idea about what they have written," he said. "When we find out, we reject the paper, but it is very difficult. In a sense, we have brought it on ourselves by insisting that any involvement by a drug company should be made explicit. They have just found ways to get round this and go undercover."[47]

> Estimates suggest that almost half of all articles published in journals are by ghostwriters. While doctors who have put their names to the papers can be paid handsomely for 'lending' their reputations, the ghostwriters remain hidden. They, and the involvement of the pharmaceutical firms, are rarely revealed.
>
> These papers endorsing certain drugs are paraded in front of GPs as independent research to persuade them to prescribe the drugs.
>
> In February the *New England Journal of Medicine* was forced to retract an article published last year by doctors from Imperial College in London and the National Heart Institute on treating a type of heart problem. It emerged that several of the listed authors had little or nothing to do with the research. The deception was revealed only when German cardiologist Dr Hubert Seggewiss, one of the eight listed authors, called the editor of the journal to say he had never seen any version of the paper.
>
> An article published last February in the *Journal of Alimentary Pharmacology*, which specialises in stomach disorders, involved a medical writer working for drug giant AstraZeneca - a fact that was not revealed by the author.
>
> The article, by a German doctor, acknowledged the 'contribution' of Dr Madeline Frame, but did not admit that she was a senior medical writer for AstraZeneca. The article essentially supported the use of a drug called Omeprazole - which is manufactured by AstraZeneca - for gastric ulcers, despite suggestions that it gave rise to more adverse reactions than similar drugs.

Alexei Koudinov, MD, PhD, neuroscientist and an editor, in response to a *BMJ* paper[48] on the uneasy relationship between medical journals and pharmaceutical companies responded in a letter:[49]

… Last week I and my colleagues were digesting May 22, 2003 *Neuron* (a major neursocience journal published by Cell press) article and associated editorial coverage[50] on a validity of the Alzheimer's amyloid-based therapy (read 'amyloid cascade hypothesis'.)

I and others found that the title and some of the conclusions of this study are not yet justified. Moreover, the authors provided an apparently false statement that "they have no competing financial interests related to Elan/Wyeth-Ayerst," a vaccine maker, creating a rationale to consider the article "a bias in favor of the expired amyloid dogma-based Alzheimer's therapy approach."

This week's *BMJ* editorial is confident that "journals are caught between publishing the most relevant and valid research and being used as vehicles for drug company propaganda." In light of the above I wonder to which category the latest *Neuron* articles on Alzheimer's disease belong to.

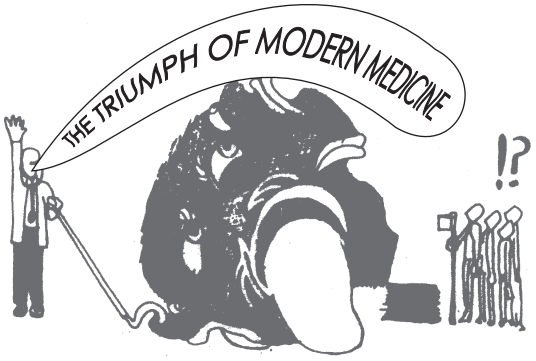
I believe that many neuroscientists are puzzled, too, especially because a similar question was earlier discussed (see below message to remember) for the consensus recommendations for the post-mortem diagnosis of Alzheimer's disease by the NIH National Institute on Aging a key citation of the *Neuron* study… (*citations in the original letter)*

Alzheimer's disease research: a message to remember

Science, and biomedical science in particular, is competitive, and for many is a pursuit that generates considerable passion and emotion. No wonder, then, that competing scientists working in the most competitive disciplines occasionally come to blows. Research into HIV and Alzheimer disease seems to suffer more than most in this respect. Judging by recent events, this reputation seems justified, at least for the Alzheimer field.

Repeating the charges and details of these cases here would only serve to highlight a small number of individuals who are in fact only a subset of a much larger community of biomedical researchers balancing the often conflicting demands of academia and commerce.

Source: *Nature Medicine*, July 1999, 5(7):713 <http://bmj.bmjjournals.com/cgi/eletters/326/7400/1202#2remember>



Source: ***Taking Sides,*** **op,.cit.**

Another more revealing response was from a former ghostwriter, Susanna Rees (see box *Who Actually Wrote the Research Paper*).

Who Actually Wrote the Research Paper? How to find it out

In reply to the *BMJ* theme issue of 31st May 2003 (Vol 326 issue 7400) "Time to untangle doctors from drug companies."[51]

Until the end of 2002, I worked for a medical writing agency as an editorial assistant. I believe that the agency I worked for generally has standards of practice that are consistent with best practice within the industry. I write to you about the broader issues associated with general practices in the industry.

It is my perception that there is consistently a high turnover in staff throughout all branches of the pharmaceutical industry. It is also my perception that the effect of this is that there is often a lack of consistent follow-through on how the pharmaceutical industry acquires data, monitors it, processes it, validates it.

Medical writing agencies go to great lengths to disguise the fact that the papers and conference abstracts that they ghost-write and submit to journals and conferences are ghost-written on behalf of pharmaceutical companies and not by the named authors. There is a relatively high success rate for ghost-written submissions - not outstanding, but consistent.

One standard operating procedure I have used states that before a paper is submitted to a journal electronically or on disk, the editorial assistant must open the File Properties of the Word document manuscript and remove the names of the medical writing agency or agency ghost-writer or pharmaceutical drug company, and replace these with the name and institution of the person who has been invited by the pharmaceutical drug company (or by the agency acting on its behalf) to be named as lead author, but who may have had no actual input into the paper.

Quality-assurance auditors vet the standard operating procedures of the agency I worked for. I am surprised that these auditors, presumably following government guidelines, do validate such a procedure, which is actually in place in order disguise the true authorship from the editorial boards of journals. This area seems very blurred. This practice is contrary to the principles of openness and transparency of the scientific method.

The full file history of every Word document may be retrieved, using a Texteditor or a Hexeditor. It is impossible to change that history or to disguise who actually created the Word document or the name of the organisation of origin. Office applications can reveal the full chronology of authors, file paths, file names, file amendments, and details of the computers used. Text, graphics or tables that have been inserted into a Word file will contain the full history of the document that they were extracted from. Technical effort is required to identify this information [1,2]. Such a check might be made prior to peer-review, using an original file, saved onto disk by the authors and included as part of the submission package to the journal. Even this check may not be exhaustive or conclusive: for example, where a file has been exported into .RTF format, much of the original file history may be lost. A Word document that has been exported into .RTF format and subsequently back into .DOC format, may possibly lose much of its original Word file history. RTF offers a "track changes" option, so it may be possible to view the entire text-editing history of a Word document that has been exported into .RTF format. A file that has been exported into .PDF format will have lost its entire history.

On-line submission of ghost-written papers and abstracts to journals and conferences is done from the agency computer or sometimes from the offices of the pharmaceutical company. Do journals and conference organisers always try to identify the organisation that actually submitted the electronic file?

An internet engine search on the authors of a paper will quickly reveal whether these names are closely linked to pharmaceutical drug companies, to their products or publicity materials.

The interests of the pharmaceutical industry lie at the heart of many current, urgent debates: GM food, anti-depressants and their side-effects, and others. We need to ask: Who wrote this paper? Who did this research? Are the objectives of this research genuinely impartial? Is this process fully transparent?....

References

(1) PC-Welt (German language publication) 1999(7): 242-243. "Verborgene Infos" (trans: Hidden information) Springer T, Apfelböck H. (2) c't (German language publication) 2002(3): 172-175. "Dokumente durchleuchtet: Was Office-Dateien verraten können" (trans: Documents under the X-ray: what Office files can tell you) Rost M, Wallisch A.

Competing interests: None declared

Source: Susanna T Rees, Care Assistant, *BMJ*, 12 June 2003. Citations in the original at <http://bmj.bmjjournals.com/cgi/eletters/326/7400/1202#33226>

3. Conflicts of Interest and Codes of Marketing

3.1 On Codes of Marketing and Behaviour

Many of the above result in conflict of interests and competing interests for researchers and doctors involved and indeed for editors of medical journals (see Annexure 2, "Conflict of Interest, My Journey" by Richard Smith.) The first step to recognizing conflict (s) of interest and competing interests is to recognize it and not pretend that one does not get influenced by research programmes and funding by drug companies. And also not think of it as a new form of political correctness that bioethicists demand nowadays. In fact, if any doctor, journalist or politician speaks for drug companies, one should immediately ask them their source of income and holidays taken.

The first step to clean the stable in India is to start at the top (and this is where the recently passed Right to Information Act may be useful).

- A declaration of conflict of interests by those in the decision-making bodies related to drugs like DTAB and DCCI.
- The Drug Controller General of India and all State Drug Controllers and drug inspectors to declare share holdings in drug companies - preferably this should be prohibited.
- All academic institutions and academics and others in position of responsibility to declare their conflict of interests before joining any Government Committees.
- A registry of clinical trials being conducted in India and persons and institutions handling the same.
- Steps by professional bodies and doctors to actively avoid and where possible formally prohibit forms of entanglement with drug companies.
- Minimising of discretionary element in decision making powers of Government drug functionaries deciding on compliance of drug laws (for example Schedule M).

3.2 Drug Industry and Voluntary Codes

It is clear that drug industry as much as the medical profession and medical journals need some kind of ethical guidelines. India does not have an official Ethical Criteria of Marketing of Medicines. WHO has been advocating *Ethical Criteria for Medicinal Drug Promotion* (World Health Organization, Geneva 1988). It is perhaps this fear of further regulation or legislation that prompted the drug industry to draft a voluntary code in 1981. The International Federation of Pharmaceutical Manufacturers (IFPMA) first issued a statement of the "obligations" of the drug industry; then it suggested a number of "general principles" by which these obligations might be fulfilled. IFPMA Code is not a global code. It specifically states that this would "impractical" because of differences in local conditions. The Code is only an attempt "to encourage" national member organisations either to introduce or to revise their own voluntary codes.

Some Figures on Lobbying Outlays by Pharma in US Congress	
Pharmaceutical Research & Manufacturers of America Lobbying 1998-2004: $72,720,000 Lobbying 2004: $15,520,000	Wyeth Lobbying 1998-2004: $24,061,926 Lobbying 2004: $4,240,000
Pfizer Inc. Lobbying 1998-2004: $43,522,720 Lobbying 2004: $5,660,000	Biotechnology Industry Organization Lobbying 1998-2004: $23,605,796 Lobbying 2004: $5,180,000
Merck & Co. Lobbying 1998-2004: $40,710,294 Lobbying 2004: $3,560,000	Amgen Inc. Lobbying 1998-2004: $22,827,500 Lobbying 2004: $3,367,500
Abbott Laboratories Lobbying 1998-2004: $27,566,000 Lobbying 2004: $4,760,000	Johnson & Johnson, Inc. Lobbying 1998-2004: $21,760,000 Lobbying 2004: $4,500,000
Eli Lilly and Co. Lobbying 1998-2004: $36,510,000 Lobbying 2004: $3,400,000	Schering-Plough Corp. Lobbying 1998-2004: $21,098,000 Lobbying 2004: $1,540,000
Bristol-Myers Squibb Co. Lobbying 1998-2004: $31,760,579 Lobbying 2004: $5,580,000	Sanofi-Aventis Lobbying 1998-2004: $19,156,712 Lobbying 2004: $3,914,000

Source: <http://www.publicintegrity.org/lobby/>

Spending Money to Change Policy: Budget Initiatives of Pharmaceutical Research and Manufacturers of America (PhRMA)

PhRMA Initiatives	Budget (US$m)
Pharmaceutical lobbying at the US federal and state level	121.4
Fighting price controls and protecting patent rights in foreign countries and in trade negotiations	17.5
Fighting a union-driven initiative in Ohio to lower drug prices for people with inadequate insurance cover	15.8
Lobbying the US Food and Drug Administration	4.9
Payments to research and policy organizations sympathetic to the industry	2.0
Funding a standing network of economists to speak against US drug price controls	1.0
Changing the Canadian health care system	1.0
TOTAL	163.6

Source: Pear R (2003). Drug companies increase spending on efforts to lobby Congress and governments. *New York Times*, June 1 <http://www.nytimes.com/2003/06/01/national/01LOBB.html?tntemail1, accessed 8 March 2005)>. Quoted in *Global Health Watch Report 2005-06,* p. 110.

The WHO finally came out with *Ethical Criteria for Medicinal Drug Promotion* in May 1988 although it was mandated to do so earlier in May 1978. The WHO has however made very little effort to distribute or propagate these ethical criteria among developing countries. The chief financier of the WHO is the US government (almost 25 per cent and with Germany and Japan included it is 45 percent) who in 1978 had withdrawn from ILO because it was getting 'highly politicised' and gave a similar reason for withdrawal from UNESCO in 1987. The WHO has fears of its financial future and it is this, which has made it probably develop cold feet with respect to the code and earlier with the Essential Drug lists.

The IFPMA Code is inadequate, as it tends to legitimize existing practices. It does not suggest improvements nor encourages improved practices. It fails to prevent companies producing inappropriate promotional materials, or utilizing unethical marketing practices.

The WHO *Ethical Criteria for Medicinal Drug Promotion* (1988) fails to adequately cover such promotional practices as offering gifts to health workers, distribution of free samples, advertising and promotion to general public, the prominence of essential information in promotional communications to health workers, the volume of promotion for less-than-essential products, and the role of the industry in continuing medical education. In addition, the WHO Criteria lacks monitoring procedures.

The Health Action International (HAI), a network of consumer, development action and other like-minded organizations, published a more comprehensive draft code on pharmaceuticals in 1981. Published as a discussion document, it is aimed at encouraging constructive discussions between all parties involved in the supply and use of pharmaceuticals. It suggests standards for drug promotion, pricing, sales, distribution, trade, technology and research and development.

The international codes or guidelines must require that corporations take full responsibility for the effect of their operations on the health, safety, economy and the environment of the host country. Such codes/guidelines will serve to assure the public that corporations agree to abide by the provisions of the code/guidelines which sets standards of decency, fair competition and greater honesty in the operations of businesses across national boundaries.

How effective are international codes in actual practice? Indeed there are limitations with regard to their implementation. For one thing, codes are only self-regulatory. They are recommendations of international bodies and their implementation depends on the co-operation of the companies and national legislations.

Corporations are known to violate the adopted codes even after agreeing to comply with the provisions sometimes blatantly and at other times subtly. For instance, the WHO/UNICEF International Code on Marketing of Breast Milk Substitutes adopted in 1981 is being violated by the babymilk industry which has devised new marketing techniques that create the appearance of compliance whilst making maximum use of grey areas in the Code. The reluctance on the part of the industry to adhere to the code is explained by the International Baby Food Action Network (IBFAN): "there is an inherent conflict between the aims of the international Code and the goals of the babyfood industry. The Code aims to protect and promote breastfeeding by preventing unethical marketing of breastmilk substitutes; this is bound to lead to a reduction in the market for babyfood."

For the effective implementation of international codes, they must be adopted with provisions for all the necessary mechanisms for their proper implementation. It is necessary that adequate funding be provided

for independent regulatory agencies. Effective international mechanisms to regulate MNCs be developed for monitoring the code violations and also for imposing sanctions against violators. Only with the provisions of such mechanisms for the effective implementation of the codes, will the codes have any real meaning (see also Annexure 3 for a more detailed comparison of the various codes on ethical marketing). In April 1997, the Indian Drug Manufacturers' Association (IDMA) came up with a draft marketing code.

The Medical Council of India has recently revised its Code of Ethics Regulations, 2002[52] and it has some useful gems such as:

- A physician should be an upright man, instructed in the art of healings. He shall keep himself pure in character and be diligent in caring for the sick; he should be modest, sober, patient, prompt in discharging his duty without anxiety; conducting himself with propriety in his profession and in all the actions of his life. (1.1.2)

- *Every physician should, as far as possible, prescribe drugs with generic names and he/she shall ensure that there is a rational prescription and use of drugs. (1.5)* (italics ours)

- The physician, engaged in the practice of medicine shall give priority to the interests of patients. The personal financial interests of a physician should not conflict with the medical interests of patients. (1.8)

- Unnecessary consultations should be avoided (3.1) (meaning cross practice and polypharmacy)

- … A physician shall not give to any person, whether for compensation or otherwise, any approval, recommendation, endorsement, certificate, report or statement with respect of any drug, medicine, nostrum remedy, surgical, or therapeutic article, apparatus or appliance or any commercial product or article with respect of any property… (6.1)

- A physician should not run an open shop for sale of medicine for dispensing prescriptions prescribed by doctors other than himself or for sale of medical or surgical appliances (6.3)

- A physician shall not give, solicit, or receive nor shall he offer to give solicit or receive, any gift, gratuity, commission or bonus in consideration of or return for the referring, recommending or procuring of any patient for medical, surgical or other treatment. (6.4.1)

- Clinical drug trials or other research involving patients or volunteers as per the guidelines of ICMR can be undertaken, provided ethical considerations are borne in mind. Violation of existing ICMR guidelines in this regard shall constitute misconduct. Consent taken from the patient for trial of drug or therapy which is not as per the guidelines shall also be construed as misconduct. (7.22)

The more the violations in real life, the stricter the code it appears. The MCI to date has not taken any disciplinary action of any significance on any doctor in India.

Annexure1

What are Clinical Trials?[53]

Clinical trials are the foundation for clinical research, especially in modern medicine.

The term clinical trial is most commonly associated with large randomized studies; many clinical trials are small. They may be initiated by single physicians, a small group of physicians, or by researchers employed by a pharmaceutical company and are designed to test simple questions. Other clinical trials require large numbers of participants followed over long periods of time. It is sometimes necessary to organize multicentre clinical trials. Often the centres taking part in such trials are in different countries (in which case they may be termed international clinical trials).

Three basic principles underlie good clinical research:

1) *Principle of Replication:* Treatment procedures should be repeated with various persons so as to confirm that a particular result was not due to accident or good fortune. Replication introduces its own errors but there are some ways of minimizing these errors.

2) *Principle of Randomization:* The clinical trial experiment should be so designed such that specific chance factors, favourable or unfavourable to some persons, are evenly distributed. This will also ensure that we do not choose similarly placed persons, or persons who we feel will respond better.

3) *Principle of Experimental Control:* This is to compare experimental results (say that of a new drug or treatment) with another identical group (who have been given the old drug or treatment).

One of the most confounding factors in clinical research that needs ruling out is the "natural or spontaneous course of a disease or condition." This is paraphrased in the quip, that common cold gets cured in a week *with* a doctor's treatment and seven days *without*.

Often a radically new drug is compared with a dummy pill or placebo. The reason why sometimes an impressive number of people get cured with dummy pills, is not understood sufficiently. It has been suggested that the psychological state of receiving medical care and treatment might lead to some tangible health benefits too. Statistical tests are always used to compare the drug/treatment being tested with a dummy pill or the older drug/treatment.

Here are some FAQs regarding clinical trials.

Whatareclinicaltrials?

"Any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome."[54] By "medical intervention" is meant any intervention used to modify a health outcome. Clinical trials are fundamental to the development of innovative medicines and vaccines for treating and preventing illnesses in both humans and animals.

Whatdoclinicaltrialsdo?

Clinical trials, also called clinical studies/protocols, help evaluate a new drug, medical device or intervention in strictly scientifically controlled settings, and are required for the DCGI's (Drugs Controller General of India) approval of new therapies. Trials may be designed to assess the safety and efficacy of an experimental therapy, to assess whether the new intervention is better than standard therapy, or to compare the efficacy of two standard or marketed interventions.

Whatisanethicalclinicaltrial?

They should have at the minimum informed consent (see below) and they should be supervised by an ethics committee. People participating in ethical clinical trials are *volunteers* and are not paid. However in some circumstances, research participants can be compensated for costs associated with participating in the trial: e.g., loss of wage, transport, etc. People should not be exploited and a volunteer's human rights must be respected all the time before, during and after the trial. The results of a clinical trial should be made available at the earliest in an ethical and scientific manner regardless of the outcome of the trial.

Whatisinformedconsent?

Informed consent is a legal condition whereby a person can be said to have given consent based upon an appreciation and understanding of the facts and implications of any action. The individual needs to be in possession of all of his/her faculties (for example, not mentally impaired or mentally ill), and his/her judgment not impaired at the time of consenting (by sleep, illness, intoxication, alcohol, drugs or other health problems, etc.).

Some acts cannot legally take place because of a lack of informed consent. In other cases, consent of someone on behalf of a person not considered able to give informed consent is valid. Examples of this include the parents or legal guardians of a child and care givers for the mentally ill. Your participation in any Clinical Center research protocol is *voluntary*.

It is good to discuss the protocol with family and friends. Please note that you should not be hurried into making a decision, and you will be asked to sign the document only after you understand the nature of the protocol and agree to the commitment. At any time after signing the protocol, you are free to change your mind and decide not to participate further. This means that *you are free to withdraw from the study completely*, or to refuse particular treatments or tests. But care of a doctor is necessary to ensure the health of the patient even after withdrawal from the study.

WhatarePhaseI,PhaseIIandPhaseIIIstudies?[55]

The Phase 1 study is used to learn the "maximum tolerated dose" of a drug that does not produce unacceptable side-effects. Patient volunteers are followed primarily for side-effects, and not for how the drug affects their disease. The first few volunteer subjects, about 20 to 80 in number, receive low doses of the trial drug to see how the drug is tolerated and to learn how it acts in the body. The next group of volunteer subjects receives larger amounts. Phase 1 studies typically offer little or no benefit to the volunteer subjects.

The Phase 2 study involves a drug whose dose and side-effects are well known. A larger group of volunteers, about 100 to 300, are tested, to define side-effects, learn how it is used in the body, and learn how it helps the condition under study. Some volunteer subjects may benefit from a Phase 2 study.

The Phase 3 study compares the new drug against a commonly used drug. In Phase 3 studies, the study drug or treatment is given to large groups of people - from 1,000 to 3,000. Some volunteer subjects will be given the new drug and some the commonly used drug. The trial is designed to find where the new drug fits in managing a particular condition. Determining the true benefit of a drug in a clinical trial is difficult. *Phase 4 studies* are done after the drug or treatment has been marketed. These studies continue testing the study drug or treatment to collect information about its effect in various populations and gather data on any side-effects associated with long-term use. Such adverse effects detected by Phase 4 trials may result in the withdrawal or restriction of a drug - recent examples include cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx).

Whatisaplacebo?[56]

Placebos are harmless, inactive substances made to look like the real medicine used in the clinical trial. Placebos allow the investigators to learn whether the medicine being given works better or no better than a lack of treatment. In many studies, there are successive time periods, with either the placebo or the real medicine. In order not to introduce bias, the patient, and sometimes the staff, is not told when or what the changes are. If a placebo is part of a study, you will always be informed in the consent form given to you before you agree to take part in the study. When you read the consent form, be sure that you understand what research approach is being used in the study you are entering.

Whatistheplaceboeffect?

Medical research is dogged by the *placebo effect* - the real or apparent improvement in a patient's condition due to "wishful thinking" by the investigator or the patient. Medical techniques use three ways to rid clinical trials of this problem. These methods have helped discredit some previously accepted treatments and validate new ones. Methods used are the following: randomization, single-blind or double-blind studies, and the use of a placebo.

Whatisrandomization?

We randomize trials to exclude selection bias. Randomization is when two or more alternative treatments are selected by chance, not by choice. The treatment chosen is given with the highest level of professional care and expertise, and the results of each treatment are compared. Analyses are done at intervals during a trial, which may last years. As soon as one treatment is found to be definitely superior, the trial is stopped. In this way, the fewest number of patients receive the less beneficial treatment.

WhyCantIChoosewhichTreatmentIGet....WhatGroupImin?[57]

The purpose of not knowing what group you are in (blinding), and being assigned to a group on the basis of *The Phase 3 study* compares the new drug against a commonly used drug. In Phase 3 studies, the study drug or treatment is given to large groups of people - from 1,000 to 3,000. Some volunteer subjects will be given the new drug and some the commonly used drug. The trial is designed to find where the new drug fits in managing a particular condition. Determining the true benefit of a drug in a clinical trial is difficult.

Arethererisksinvolvedinparticipatinginclinicalresearch?

The question is moot, because part of the research question is also to find out about the safety (and degree of risk-freeness of a drug or treatment). Risks are involved in clinical research, as in routine medical care. New drugs may have adverse drug reactions not known some have adverse drug reactions and side-effects that are not known to the researchers too and occur for the first time. Many risks can be predicted from experience in animal studies. However some risks tend to be latent and emerge only years after.

Most clinical studies pose risks of minor discomfort, lasting only a short time. Some volunteer subjects, however, experience complications that require medical attention. The specific risks associated with any research protocol are described in detail in the consent document, which you are asked to sign before taking part in research. In addition, a member of the research team, who will answer your questions about the study, will explain the major risks of participating in a study to you. Before deciding to participate, you should carefully weigh these risks. Although you may not receive any direct benefit as a result of participating in research, the knowledge developed may help others.

Whataresomeotherissuesinclinicalresearch?

The list is too long to mention and after so many books and papers and seminars on the subject. There is no consensus on many issues regarding clinical trials and studies except probably clinical that research needs to be ethical, free of conflicts of interest, and should respect human rights. In recent years there has been some discussion also on the need to have more clinical trials of drugs, which are relevant to the needs of the Low and Middle Income countries. This is especially relevant in a context where there is a significant outsourcing taking place to countries like India, where companies in the West are conducting clinical trials for drugs to be marketed in the West, in poorer countries.

Arethereothertypesofmedicalenquiry?

Yes of course. The double-blind clinical trial we have described is of the simplest type in design. There are many modifications in details of the double-blind trial to accommodate the removal of various types of biases; there are trials in which the patient is used as his or her own control (cross-over design); other forms go by names like controlled trials with matched pairs, sequential analysis, etc.

Clinical trials involve patients directly and therefore they may be called in experimental in nature. Other types of studies are population-based and they include cross-section studies, case-control studies, cohort studies, etc. The major difference between clinical trials and population-basesd or epidemiological studies is that, in clinical trials, the investigators manipulate the administration of a new intervention and measure the effect of that manipulation, whereas epidemiological studies only observe associations (correlations) between the treatments experienced by participants and their health status or diseases.

For further information, please look at:

Bandolier Professional. *Independent Evidence-based Health Care. On Quality and Validity* at <www.ebandolier.com>, <http://www.cc.nih.gov>, <http://www.clinicaltrials.gov>, <http://www.genome.gov>, <http://www.inova.org>, <http://www.multiplemyeloma.org/clinical_trials>, <http://hivinsite.ucsf.edu>, <http://en.wikipedia.org/wiki/Clinical_trial>

- Rang HP, Dale MM, Ritter JM, Moore PK (2003). *Pharmacology* 5 ed. Edinburgh: Churchill Livingstone.
- *A Dictionary of (Ecological) Epidemiology* Copyright Jonathan Swinton 1998-2002 <http://www.swintons.net/jonathan/Academic/glossary.html>
- The WWW Virtual Library: Medicine and Health: Epidemiology <http://www.epibiostat.ucsf.edu/epidem/epidem.html>
- *Indian Journal of Medical Ethics*, *Selected Readings 1993-2003*, Mumbai, Nov 2005.
- And also the website of *Indian Journal of Medical Ethics* (http://www.issuesinmedicalethics.org)

Annexure2

Conflict of Interest: My Journey[58]

Richard Smith, former Editor, *BMJ*

How Common are Competing Interests?

- A quarter of US researchers have received pharmaceutical funding.
- Half have received "research related gifts."
- An analysis of 789 articles from major medical journals found that a third of the lead authors had financial interests. in their research patents, shares, or payments for being on advisory boards or working as a director.

Bekelman JE, Li Y, Gross CP. "Scope and impact of financial conflicts of interest in biomedical research. A systematic review." *JAMA* 2003; 289: 454-65.

How Common are Competing Interests?

- 75 pieces giving views on calcium channel blockers.
- 89 authors
- 69 (80%) responded
- 45 (63%) had financial conflicts of interest.
- Only 2 of 70 articles disclosed the conflicts of interest.

Stelfox HT, Chua G, O'Rourke K, Detsky AS. "Conflict of interest in the debate over calcium channel antagonists." *N Engl J Med* 1998; 338: 101-105

Do Authors Declare Conflicts of Interests?

- 3642 articles in the five leading general medical journals (*Annals of Internal Medicine, BMJ, Lancet, JAMA,* and the *New England Journal of Medicine*)
- Only 52 (1.4%) declared authors' conflicts of interest.

Hussain A, Smith R. "Declaring financial competing interests: survey of five general medical journals." *BMJ* 2001; 323:263-4.

Does Conflict of Interest Matter?

- 11 studies compared the outcome of studies sponsored by industry and those not so sponsored.
- In every study those that were sponsored were more likely to have a finding favourable to industry.
- When the results were pooled the sponsored studies were almost four times more likely to find results favourable to industry.

Bekelman JE, Li Y, Gross CP. "Scope and impact of financial conflicts of interest in biomedical research. A systematic review." *JAMA* 2003; 289: 454-65.

Does Conflict of Interest Matter?

- 106 reviews, with 37% concluding that passive smoking was not harmful and the rest that it was.
- Multiple regression analysis controlling for article quality, peer review status, article topic, and year of publication found that the only factor associated with the review's conclusion was whether the author was affiliated with the tobacco industry.
- Only 23% of reviews disclosed the sources of funding for research.

Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. *JAMA* 1998; 279: 1566-1570

Does Conflict of Interest Matter? Third Generation Contraceptive Pills

- At the end of 1998 three major studies without sponsoring from the industry found a higher risk of venous thrombosis for third generation contraceptives; three sponsored studies did not.
- To date, of nine studies without sponsoring, one study found no difference and the other eight found relative risks from 1.5 to 4.0 (summary relative risk 2.4); four sponsored studies found relative risks between 0.8 and 1.5 (summary relative risk 1.1) .
- The sponsored study with a relative risk of 1.5 has been reanalysed several times, yielding lower relative risks; after this failed to convince, a new reanalysis was sponsored by another company.
- One sponsored study finding an increased risk has not been published.

Vandenbroucke JP, Helmerhorst FM, Frits R Rosendaal FR. Competing interests and controversy about third generation oral contraceptives. *BMJ* 2000; 320: 381.

Sponsored Research

- A systematic review found 30 studies that compared research funded by drug companies research funded by other sources
- Company sponsored research more likely to be published
- Studies sponsored by pharmaceutical companies were more likely to have outcomes favouring the sponsor than were studies with other sponsors (odds ratio 4.05; 95% confidence interval 2.98 to 5.51; 18 comparisons)
- None of the 13 studies that analysed methods reported that studies funded by industry was of poorer quality

Joel Lexchin, Lisa A Bero, Benjamin Djulbegovic, and Otavio Clark. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ*, May 2003; 326: 1167 - 1170.

What Proportion of Trials in the five Major General Journals are Funded by Industry?

- 75% in *Annals of Internal Medicine, Lancet, JA*MA, and *NEJM*
- 30% in *BMJ*

NatureNeuroscience and Conflict of Interest

- Charles Nemeroff, professor of neuropsychopharmacology at Emory University School of Medicine, Atlanta, published a review on mood disorders in the February issue of *Nature Neurosciences.*
- Declared no conflicts of interest.
- But he held a patent on a transdermal lithium patch that the review mentioned favourably.
- Member of the scientific advisory board of Corcept Therapeutics, a company carrying out trials with mifepristone, which was mentioned favourably in the review, and as such, was given an option to purchase 72 000 shares at a total cost of $21.60.
- Director and chairman of the psychopharmacology advisory board of *Cypress Bioscience*, which has only one product milnacipran which was mentioned in the review.

Annexure3

WHO Ethical Criteria and IFPMA Code of Pharmaceutical Marketing Practices - Review and Comment

WHO:OnPromotion

Active promotion within a country should take place only with respect to drugs legally available in the country. Promotion should be in keeping with national health policies and in compliance with national regulations, as well as with voluntary standards where they exist. All promotion making claims concerning medicinal drugs should be reliable, accurate, truthful, informative, balanced, up to date, capable of substantiation and in good taste. It should not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable drugs use or to give rise to undue risks. The word safe should only be used if properly qualified. Comparison of products should be factual, fair and capable of substantiation. Promotional material should not be designed so as to disguise its real nature.

IFPMA:OnPromotion(Obligations)

The industry in general obligations, undertook to ensure that all products it makes available for prescription purposes to the public are backed by the fullest technological service and have full regard to the needs of public health; to produce pharmaceutical products under adequate procedures and strict quality assurance; to base the claims for substances and formulations on valid scientific evidence, thus determining the therapeutic indications and conditions of use; to provide scientific information with objectivity and good taste, with scrupulous regard for truth, and with clear statements with respect to indications, contraindications, tolerance and toxicity; to use complete candour in dealings with public health officials, health care professionals and the public.

HAIComments:OnPromotion

(1) The promotion of prescription only products should not be permitted directly or indirectly to the general public. (2) The usefulness of the promotion of OTC products to the general public is in some doubt, as many of these products are for trivial or self-limiting conditions and are often of doubtful efficacy. Their promotion encourages pill for every ill mentality which detracts from preventive health care, wastes resources and can expose common consumers to unnecessary risks. Thus, promotion of OTC products to the general public should not be permitted. (3) Promotion to health workers must be consistent with existing national health and drugs policies, taking into account recommended treatment regimes, where these are in effect. (4) The volume of promotion for a particular product must be consistent with that product's utility in treating the major disease conditions prevalent in a particular country. Promotion of products for self-limiting or trivial conditions should not be permitted. (5) As no drug is completely without risk, the word safe with or without qualification, should not be permitted in any promotional material. (6) All promotion for pharmaceutical products must be accurate, factual, balanced and up to date. It must conform to legal requirements and to standards of good taste, and be provided in a language readily understandable to the person who will use it. It must not mislead, either directly or by implication, by omission or information, or by unverifiable statements.

WHO:OnAdvertisementstotheGeneralPublic

Advertisements to the general public should help people to make rational decisions on the use of drugs determined to be legally available without a prescription. While they should take account of people's legitimate desire for information regarding their health they should not take undue advantage of people's concern for their health. They should not generally be permitted for prescription drugs or to promote drugs

for certain serious conditions that can be treated only by qualified health practitioners, for which certain countries have established lists. While health education aimed at children is highly desirable, drug advertisements should not be directed at children. Advertisements may claim that a drug can cure, prevent, or relieve an ailment only if this can be substantiated. They should also indicate, where applicable, appropriate limitations to the use of the drug.

IFPMA:OnAdvertisementstotheGeneralPublic

Not covered by the IFPMA Code. The World Federation of Proprietary Medicine Manufacturers (WFPMM) has, however, developed guidelines for the production of voluntary codes of advertising practice.

HAIComments:OnAdvertisementstotheGeneralPublic

(1) As mentioned above, advertisements to the general public for non-prescription drugs should not be permitted. There is a clear acceptance by the industry that advertising aimed at children is certainly not ethical or advisable. A recent study by the Association of British Pharmaceutical Industries found the average British patient has a reading age of nine. Thus, it is difficult to justify promotion of any drugs to the public. (2) If public advertising is permitted, all advertisements must not be directed at children. (3) If public advertising is permitted, all advertisements must carry a clear and prominent statement advising users of the products to read and follow the instructions for use on the package, label or package insert of the product, and if they are unsure of what any of the directions mean, to consult a physician or pharmacist before taking the product. (4) If public advertising is permitted, advertisements for products that should be avoided during pregnancy and lactation should contain graphic warning symbols.

WHO:OnSamples

Free samples of legally available prescription drugs may be provided in modest quantities to prescribers, generally on request. Countries vary in their practices regarding the provision of free samples of non-prescription drugs to the general public, some countries permitting it, some not. Also a distinction has to be made between provision of free drugs by health agencies for the care of certain groups and the provision for free samples to the general public for promotional purposes. The provision of free samples of non-prescription drugs to the general public for promotional purposes is difficult to justify from a health perspective. If this practice is legally permitted in any country, it should be handled with great restraint.

IFPMA:OnSamples

Samples may be supplied to the medical and allied professions to familiarise them with the products, to enable them to gain experience with the product in their practice, or upon request. The IFPMA Code does not deal explicitly with samples to the general public. The WFPMM Guidelines do not mention sampling to the public.

HAIComments:OnSamples

(1) The routine provision of samples of prescription or non-prescription drugs to health workers, health institutions, or the general public should not be permitted. (2) Supplies of prescription drugs, in sufficient quantity for controlled and approved clinical trials, or other legitimate research, may be permitted.

WHO:OnSymposiaandotherScientificMeetings

Symposia are useful for disseminating information. The objective scientific content of such meetings should be paramount and presentations by independent scientists and health professionals are helpful to this end. Their educational value may be enhanced if they are organised by scientific or professional bodies. The fact of sponsorship by a pharmaceutical manufacturer or distributor should be clearly stated in

advance, at the meeting and in any proceedings. The latter should accurately reflect the presentations and discussions. Entertainment or other hospitality and any gifts offered to members of the medical and allied professions should be secondary to the main purpose of the meeting and should be kept to a modest level.

IFPMA:OnSymposiaandotherScientificMeetings

Symposia, congresses and the like are indispensable for the dissemination of knowledge and experience. Scientific objectives should be the principal focus in arranging such meetings, and entertainment and other hospitality shall not be inconsistent with such objectives.

HAIComments:OnSymposiaandotherScientificMeetings

1) The organisation by pharmaceutical manufacturers or distributors of symposia and other scientific meetings should only be permitted if approval for such a meeting has been granted by the relevant national or international health worker association, health institution or government department, an independent panel of scientists and/or health workers has been set up to review the content of the meeting, and full disclosure of the sponsorship is stated in all communications related to the meeting, and at the meeting itself. (2) Partial sponsorship of such meetings may be permitted if such sponsorship is requested by the organisers, subject to the full disclosure of the sponsorship.

Source: Kanji, Najmi, et al. *Drugs Policy in Developing Countries.* London: Zed Books, 1992, pp.128-131.

Illustration: Anthony Flores in PLoS Med *3(4): e191*

Endnotes

[1] Documented in: Adams, Stanley. 1984. *Roche Versus Adams*. London: Jonathan Cape.

[2] *New York Times*: "Doctor who testifies against Merck is demoted at Cleveland Clinic's Medical College" at <http://www.nytimes.com/2005/12/10/business/10vioxx.html>.

[3] There is a vast literature documenting these "forms of entanglement". See for instance:

1) "Marketing of Medicines in India: Informing, influencing or inducing?" 3 Apr 2004 *BMJ*, Editorial by Chandra M.Gulhati.
2) Blumenthal, David. "Doctors and Drug Companies", *N Engl.J Med*, 351:1885-1890, October 28, 2004, Number 18.
3) Moynihan, Ray: "Who pays for the pizza? Redefining the relationships between doctors and drug companies. " *BMJ* 2003; 326:1189-1192.

[4] Moynihan, "Who pays for the pizza?", op.cit. Reproduced for fair use.

[5] K.R.Sethuraman, Professor of Medicine, JIPMER, Pondicherry, in response to Chandra M.Gulhati's *BMJ* editorial, "Marketing of Medicines in India: Informing, influencing or inducing?" 3 Apr 2004 *BMJ*.

[6] Gitanjali, B., C H Shashindran, K D Tripathi, K R Sethuraman. "Are drug advertisements in Indian edition of *BMJ* unethical?" *BMJ* 1997; 315:459.

[7] *Time* magazine website, "Fighting the freebies", G.Jeffrey Macdonald, Nov. 06, 2005.

[8] See <http://www.nofreelunch.org/>.

[9] For more details, see <http://www.nofreelunch.org/>.

[10] Presentation by Dr C.M.Gulhati, Editor, *MIMS India*, at Kolkata Seminar on Rational Drug Use organized by JSA, FMRAI, AIDAN, et al., April 2005. Reproduced with permission.

[11] Quoted by Dr Gulhati, op.cit., April 2005 and personal communication, November 2005.

[12] Source: *Hindustan Times*, December 31, 2003 quoted in Gulhati, op.cit.

[13] Gulhati, April 2005, op.cit.

[14] Gulhati, April 2005, op.cit. Reproduced with permission. Conferences mentioned were held between 2002-03.

[15] House of Commons Report on *The Influence of the Pharmaceutical Industry*, 2004-05. <www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/42/42.pdf>

[16] Source: "Unending Q of Unethical Drug Trials," Editorial in *MIMS India*, Feb 2004. See also: Nundy, Samiran and Gulhati, Chandra M. "A New Colonialism? Conducting Trials in India". *N Engl.J Med* 352; 16, April 21, 2005. See also Gulhati's article in the *Indian Journal of Medical Ethics,* Jan-Feb 2004.

[17] "Johns Hopkins admits scientist used Indian patients as guinea pigs". *BMJ* 2001; 323:1204 (24 November). Also see: "The truth of the 'drug' trials". *Frontline,* Volume 18, Issue 24, Nov. 24 - Dec. 07, 2001.

[18] "A Case of Betrayal", *Frontline,* Volume 22 - Issue 25, Nov. 05 - 18, 2005. In the same issue a related report, "A award and some claims" reported:

> An innocuous statement published in a few newspapers in July should have caused a sensation in India and abroad. But it did not.
>
> It was issued by Dr. M. Krishnan Nair, the former Director of the Regional Cancer Centre, Thiruvananthapuram, to announce that a scientific paper titled 'Five year survival results of a single group study of intralesional tetra-O-methyl nordihydroguiaretic acid in oral squamous cell carcinoma (M4N study)' has been awarded the 'Best Clinical Award' in the 10th International Congress on Oral Cancer held in the Island of Crete in Greece and the authors have been awarded a cash prize of 1000 euros.
>
> "In this particular study the authors were able to obtain the best relapse-free survival at five years compared to all historic data on this cancer that too with a short exposure to M4N. The Food and Drug Administration of USA has approved this drug for clinical use," the note sent to newsrooms on July 7 said. It ended cryptically, explaining the significance of the award: "It may be noted that a great hue and cry was raised by two doctors in Regional Cancer Centre along with a few members of the lay public in the media in Kerala about the use of this drug."

[19] *MIMS India*, op.cit.

[20] Full text available at <http://finance.senate.gov/hearings/testimony/2004test/111804dgtest.pdf>. Reproduced in full as Annexure 6, Chapter 3 of this book.

[21] "Drug firms accused of distorting research", September 10, 2001, *The Guardian*. For the complete statement see, "Sponsorship, Authorship, and Accountability", *JAMA*, Vol. 286, No. 10, September 12, 2001 and at <http://jama.ama-assn.org/issues/v286n10/ffull/jed10056.html>. The signatories were: Frank Davidoff, MD editor emeritus, *Annals of Internal Medicine*; Catherine D. DeAngelis, editor, *JAMA*, MD, MPH; Jeffrey M. Drazen, MD, editor-in-chief, *New England Journal of Medicine*; John Hoey, MD, editor, *Canadian Medical Association Journal*; Liselotte Højgaard, MD, DMSc, editor-in-chief, *Tidsskrift for Den norske laegeforening* (*Journal of the Norwegian Medical Association*); Richard Horton, FRCP, editor, *The Lancet*; Sheldon Kotzin, MLS, executive editor, MEDLINE/Index Medicus; M. Gary Nicholls, MD, editor, *New Zealand Medical Journal*; Magne Nylenna, MD, editor-in-chief, Norwegian Medical Association; A. John P. M. Overbeke, MD, PhD, executive editor, *Nederlands Tijdschrift voor Geneeskunde* (*Dutch Journal of Medicine*); Harold C. Sox, MD, editor, *Annals of Internal Medicine*; Martin B. Van Der Weyden, MD, FRACP, FRCPA, editor, *The Medical Journal of Australia*; Michael S. Wilkes, MD, PhD, editor, *WJM Western Journal of Medicine*. The authors were members of the International Committee of Medical Journal Editors.

[22] Statement by 13 editors, op.cit.

[23] Reported in *The Guardian*, as cited before.

[24] Statement by 13 editors, op.cit.

[25] Horton R. "The Dawn of McScience". *New York Rev Books*. 2004; 51(4):7-9. Quoted in Smith, op.cit.

[26] Richard Smith. "Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies." *PLoS Medicine*, Vol 2, Issue, May 2005. And at <http://medicine.plosjournals.org>

[27] a) Rochon PA, Gurwitz JH, Simms RW, Fortin PR, Felson DT, et al. (1994). "A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis."*Arch Intern Med* 154: 157163.

B) Lexchin J, Bero LA, Djulbegovic B, Clark O (2003). " Pharmaceutical industry sponsorship and research outcome and quality." *BMJ* 326: 11671170.

[28] Quoted in: Ida Sim and Don E. Detmer. 'Beyond Trial Registration: A Global Trial Bank for Clinical Trial Reporting". *PLOS,* Volume 2, Issue 11, Nov 2005.

[29] New York Supreme Court (2004). People of the State of New York v. GlaxoSmithKline. New York: New York Supreme Court. Available online.

[30] 1) Topol EJ (2004). "Failing the public health - Rofecoxib, Merck, and the FDA." *N Engl J Med*, 351: 17071709.

2) Mathews A, Martinez B (November 1, 2004). "E-mails suggest Merck knew Vioxx's dangers at early stage." *Wall Street Journal* Sect A 1.

3) Psaty BM, Furberg CD (2005). "COX-2 inhibitors - Lessons in drug safety". *N Engl J Med*, 352: 11351135. All above references quoted in Sim and Detmer op.cit.

4) "Documents Suggest Merck Tried to Censor Vioxx Critics" at <http://www.npr.org>

[31] <http://www.vaccinationnews.com/DailyNews/June2002/CriticsSay26.htm>. See also "Phase IV Trials Real and Bogus' in *The Truth about the Drug Companies*, Chapter 9, pp.161 ff.

[32] Affidavit of Gurkirpal Singh, MD (Adjunct Clinical Professor of Medicine, Department of Medicine, Division of Gastroenterology, Stanford University School of Medicine and Chief Science Officer, Institute of Clinical Outcomes Research and Education), Senate hearing on Vioxx. Online at <http://finance.senate.gov/hearings/testimony/2004test/111804GStest.pdf>.

[33] Joel R Lexchin. "Implications of Pharmaceutical Industry Funding on Clinical Research." *Ann. Pharmacother.*, Jan 2005; 39: 194-197.

[34] House of Commons Report on *The Influence of the Pharmaceutical Industry*, 2004-05, op.cit., pp.50-51

[35] "Illegal, Unethical Promotion Hits New Highs: Indications Increased, Side Effects Suppressed", *MIMS India*, July 2005, Editorial. See also "Piracetam and Down Syndrome" at <http://www.ds-health.com/piracet.htm>.

[36] Source: *MIMS India*, July 2005, Editorial, op.cit.

[37] "Heptatitis-B firms get a shot in the arm: Centre's move to include vaccine in national immunisation plan to boost demand 300%." *Business Standard, Sep 15, 2005*. See also "Letter to Health Minister on Hepatitis B Vaccine: Why we don't need to give It for all newborns". *mfc bulletin,* Oct 2005-Jan 2006. Reprinted on pp 502-04 of this book.

[38] This and the next four instances are from: Parry, Vince. "The Art of Branding a Condition." *Medical Marketing & Media*, May 1, 2003. Quoted also in *BODHI,* 57, Mar-Apr 2004, Editorial, "Branding Human Miseries". Also available at <http://offlinehbpl.hbpl.co.uk/Misc/MMM/Features/CONDITION.pdf>.

[39] "Serotonin and Depression: A Disconnect between the Advertisements and the Scientific Literature", *PLOS Medicine,* Volume 2, Issue 12, December 2005.

[40] In 1965, Joseph Schildkraut put forth the hypothesis that depression was associated with low levels of norepinephrine and later researchers theorized that serotonin was the neurotransmitter of interest.

[41] Kravitz RL, Epstein RM, Feldman MD, Franz CE, Azari R, et al. (2005) "Influence of patients' requests for direct-to-consumer advertised antidepressants: A randomized controlled trial". *JAMA* 293: 19952002. Quoted in Lacasse and Leo, op.cit.

[42] Valenstein ES (1998). *Blaming the brain: The truth about drugs and mental health.* New York: Free Press. 292 p. Quoted in Lacasse and Leo, op.cit.

[43] Lacasse and Leo, op.cit.

[44] Parry, op.cit.

[45] This and the following two examples are from: Ray Moynihan, Iona Heath, David Henry, and Peter C Gøtzsche. "Selling sickness: the pharmaceutical industry and disease mongering". *BMJ* 2002; 324:886-891 (13 April). See also: Ray Moynihan and Alan Cassels, *Selling Sickness: How the World's Pharmaceutical Companies are Turning us into Patients*. New York: Nation Books, 2005.

[46] See<http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm> as also <http://www.injuryboard.com/view.cfm/Topic=640>

[47] "Pharmaceutical giants hire ghostwriters to produce articles - then put doctors' names on them ", Antony Barnett, public affairs editor, December 7, 2003, *The Observer*, and at <http://observer.guardian.co.uk/uk_news/story/0,6903,1101680,00.html>

[48] "Medical journals and pharmaceutical companies: uneasy bedfellows" in *BMJ*, 31st May 2003 (Vol 326, issue 7400),

[49] Richard Smith, *editor,* <http://bmj.bmjjournals.com/cgi/content/full/326/7400/1202>. Richard Smith, op.cit.

[50] 1. Hock C, *et al.* Report: "Antibodies against ?-Amyloid Slow Cognitive Decline in Alzheimer's Disease". *Neuron.* 38, 547-554 (22 May 2003).
2. Winblad B, Blum KI. Preview: "Hints of a Therapeutic Vaccine for Alzheimer's?"*Neuron.* 38, 517-8 (22 May 2003)

[51] "Medical journals and pharmaceutical companies: uneasy bedfellows" in *BMJ*, op.cit.

[52] See <http://www.mciindia.org/know/rules/ethics.htm>. Yet to become official law.

[53] Feedback of Dr Anant Bhan, bioethicist and independent researcher, Pune, on an earlier draft, is gratefully acknowledged.

[54] Definition from "Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors" at <http://www.annals.org/cgi/reprint/141/6/477.pdf >

[55] Adapted from < http://www.cc.nih.gov> and <http://www.genome.gov>. Copied for fair use in public interest.

[56] This and the next five FAQs are reproduced from < http://www.cc.nih.gov>. Copied for fair use in public interest.

[57] Copied for fair use in public interest from <http://www.inova.org/inovapublic.srt/researchedu/ire/faqs.htm>

[58] These are some of the 34 slides in a power point by the former Editor of *BMJ;* ppt at < www.bmj.com/talks>, accessed Nov 15, 2005.

Chapter 6
Patents, Trade and Availability of Medicines

… under conditions of globalization Western knowledge systems have sought, largely with success, to gain complete dominance across the globe in nearly all spheres of life. The economists' conceptions of growth, poverty, scarcity, and development, marketed by all the social sciences, have come to predominate everywhere, and the sum total of Western social science has not only been to mire the so-called developing world in ever more acute levels of poverty, but to forestall the possibility of worldviews and lifestyles that do not synchronize with the conception of the "good life" that prevails in the "developed" West. The entire theory of development…is predicated on a time-lag: countries that are under-developed or part of the developing world seek to emulate the developed countries, but by the time they have seemingly caught up, the developed countries have gone well beyond to another plane of development. The natives, to speak in a different tongue, always arrive late at the destination; indeed, the theory of development condemns the underdeveloped to live not their own lives, but rather to fulfill someone else's conception of life. Development doesn't merely demand that the past of the native be entirely jettisoned, it also hijacks the native's future.

-*Vinay Lal,* "Home Truths and McData"[1]

He, who receives an idea from me, receives instruction himself without lessening mine; as he who lights his taper at mine, receives light without darkening me.

-*Thomas Jefferson*

If I have seen further it is by standing on the shoulders of giants.

- *Isaac Newton*, Letter to Robert Hooke, February 5, 1675

Consistent with human rights norms requiring access to essential medicines and in response to Thai activist demands, Thailand has initiated a program of universal access to government-subsidized antiretroviral drugs that now reaches 70,000 of 170,000 Thai people living with HIV/AIDS. However, the future costs of expanded treatment with newer patented medicines will be prohibitive if the US. succeeds in its objectives to ratchet-up intellectual property protections. Therefore, we join our Thai colleagues at Chiang Mai and throughout Thailand demanding that the US suspend negotiations on intellectual property rights and that it drop all intellectual property provisions affecting access to pharmaceutical products, specifically all TRIPS-plus terms, in the Thai FTA and in other FTAs as well. In addition, we demand that the U.S. publish its proposed text for the entire FTA and that the Thai people have had a chance to hold public consultations on the proposed agreement.

- *International NGO Solidarity Statement*[2]

1. Free Trade, WTO/TRIPS and the Pharma Industry

Freedom of "Free" Trade

It is clear we need trade -- unless we believe and live in some kind of self-sufficient and self-reliant village republic. Among the great debates of our times - on which the jury is still out - is the question of how free should be trade in the light of globalization. Does free trade necessarily mean free capital flows? Why does it not imply free migration of labor for instance or free exchange if information? Is trade, and free trade at that, always fair to the poor?

Let us set aside for the time being troubling issues like the "inevitability" of globalization, the pattern of development -- and with it questions like development for what -- that free trade may bring; and let us also assume for the purposes of this chapter that trade and free trade are indeed benign instruments -- as many distinguished economists[3] assure us -- for alleviation of poverty and more positively for bringing prosperity to the whole world.

The idea of intellectual property rights that imply not only the right to own and sell ideas, but also the right to regulate their subsequent use is itself a major cause of market failure. Much of the discussion below is on how India's new patents amendments would affect availability of affordable drugs, both generics and new ones, nationally and globally.

Free trade the way it is conducted today is seldom fair to the poor. Free trade itself is selectively implemented by the developed countries. As of today free trade does not imply free migration of labor, for instance, or free exchange of information. They want you to buy their goods and buy your services but do not want your poor.[4] As the December 2005 Hongkong round of WTO negotiations showed, governments of developed countries would want the developing countries to remove subsidies and tariffs with alacrity but would not respond in equal measure.

We suggest that under such a framework of free trade, the idea of patents and intellectual property rights is an anomaly and acts actually as a barrier to trade.

1.1 Issues in Free Trade, IP and Innovation: Unsettled Still

Almost all justification for the positive benefits of international trade traces its roots to the British 19th century thinker David Ricardo and his theory of comparative advantage. In a by now oft-quoted illustration, Ricardo explained how it was advantageous for England to produce cloth and Portugal to produce wine, as long as both countries traded freely with each other, even though Portugal might have produced both wine and cloth at a lower cost than England did. Few have dared to question the context of Ricardo or the wisdom that trade and free trade at that is always advantageous to all parties concerned. Economist Utsa Patnaik however has this to say:[5]

> …Comparative advantage is the reason given, for example, by Professor K N Chaudhuri in the *Cambridge Economic History of India* to explain why from being the world's largest exporter of cotton textiles in the pre-colonial era, India turned into an importer of cotton manufactures from Britain and an exporter of agricultural products like raw cotton, jute, opium, indigo and so on…

> No argument can be more fallacious than Ricardo's theory. Why it should have been necessary to use military force to induce countries like Portugal, China or India to trade, if it was so beneficial for them, is not explained. Even more important, the theory is internally logically fallacious. A fallacy in a theory can arise either because the premise is incorrect, or because the argument is incorrect. In the case of the comparative advantage theory applied to Northern trade with warmer lands, the premise itself is incorrect. The premise is that in the pre-trade situation (assuming the standard two-country two-commodity model) both countries can produce both goods. Given this premise, then it can be shown that both the countries gain by specializing in that good which it can produce at relatively lower cost compared to the other country, and trading that good for the other good: for compared to the pre-trade situation, for a given level of consumption of one good a higher level of consumption of the other good results in each country. This mutual benefit arising from comparative advantage, is adduced as both the reason for and the actual outcome of specialization and trade…
>
> …While Ricardo's explanation was superficially extremely clever, he did a signal disservice to the cause of objectivity and science, by pretending in effect that all trade including forced trade, was freely chosen trade determined by technologically determined, neutral cost factors. Trade patterns which had been in reality the outcome of trade wars, genocide and political subjugation, were discussed in such a way as to ignore this historical reality of "capitalism's blustering violence" (to use a memorable phrase first employed by Rosa Luxemburg [5]); and by focusing only on value-neutral cost factors - necessarily in a fallacious manner - Ricardo provided an intellectual justification for, and hence an apologetic for forced trade. "Capitalism's blustering violence" was neatly sanitized into the theory of relative costs. All subsequent mainstream trade theory has been similarly tautological and apologetic in character, and has talked of mutual gains from trade as the necessary cause and result of all observed patterns of specialization- not simply that between countries of similar economic strength. "Factor endowments" are talked of while completely ignoring the real differences in productive capacities in the same "factor", land, in different countries. Many generations of third world economists have been fooled into believing that somehow being involved in a particular pattern of primary sector specialization, was unavoidable in terms of pure cost-of - production logic and was to the ultimate benefit of their countries...[6]

Even many economists who have been involved, enthusiastically, in the genesis of WTO see TRIPS as an unnecessary intrusion in WTO. It was only the corporate lobbies supported by the US government that succeeded in "turning it away from its trade mission and rationale and transforming it into a royalty collection agency."[7] Secondly, it is not even clear - not even to many of the World Bank experts who advocate these policies - that openness in trade promotes growth![8] Just as it is not clear that lower taxes promote investment and growth.

One of the reasons given for high prices of drugs by pharma majors is the cost of discovering a new drug. However it has been shown that many a drug including all the recent blockbusters was first discovered in public funded institutions.[9] It is also not clear at all that there is sufficient evidence to say patent protection promotes innovation. In fact IP protection has been shown to discourage future innovations.[10] At the best of times, a patent appears to be a means for creating a monopoly, and a kind of protectionism sought with rent collection in the name of royalties and profits.

Why then is the WTO refereeing free trade, not really fair trade, trade that is fair to the millions of poor primary producers? Is free trade possible in health and pharmaceuticals given the WTO/TRIPS dispensation? Is free trade and free market possible even in principle given the nature of health care

services? And can they ever lead us to equitable health services? We try and address these and related issues below.

Firstly it should be clear that the kind of people behind WTO and related multi-lateral institutions are persons who are Market Fundamentalists trying to nuke the world with their version of Mc-Jehad.[11] There is a neat revolving door between the transnational corporate world and these institutions. They mostly till the other day supported, and many still do, what is called the "Washington Consensus"[12] and left to them would like to turn the world into a super-super Wal-Mart. In fact they are convinced we are heading that way.[13] Many of these are not only market fundamentalists but also avowed protectionists in the garb of trying to protect intellectual property rights, especially when it comes to making medicines available and affordable.

We ask the question what happens to health, and the poor at that, in this ambience.

1.2 Free Trade, WTO and Health

When it comes to health, the current dominant philosophy of free trade and open markets takes on one or more of the following forms:[14]

- Acceding to TRIPS supervised by WTO and with it the idea of stricter patent protection to medicines among others.

- Opening up health and other service sectors to trade under GATS (General Agreement on Trade and Services). GATS has been described as "the first multilateral agreement to provide legally enforceable rights to trade in all services" and "the world's first multilateral agreement on investment, since it covers . . . every possible means of supplying a service, including the right to set up a commercial presence in the export market." According to the EU, GATS "aims to end arbitrary regulatory intervention, and assure predictability of laws, to generate growth in trade and investment." This means you cannot independently regulate the services sectors of your country, especially foreign service providers in India, once you have "offered" it to international trade; GATS ensures liberalized services of a particular sector in a country does not "slip back." Once health services are offered under GATS, a country loses its ability to control the many players, now national and international, in the privatization of health services.

- Accession to the Agreement on Applications of Sanitary and Phytosanitary Measures (SPS) covering food safety and regulations governing human, animal and plant health. And chalk out measures for harmonisation of quality standards in drug production and phyto-chemical and sanitary standards.

- Thus any measure a government takes to protect human, animal or plant life or health should be based on international standards, guidelines and recommendations drawn up by recognised bodies such as the FAO/WHO Codex Alimentarius Commission that deals with foods, hormones and additives. Any country wishing to implement stricter standards has to base them on scientific risk assessment. It has been known that the Codex Commission has long been dominated by representatives of the industries for which the Commission sets standards (although the industry

representatives attend as part of a WTO member country's delegation).

- The Agreement on Technical Barriers to Trade (TBT) encourages countries to use internationally-agreed standards for their technical regulations but the regulations cannot be more "trade restrictive" than necessary. It does not identify the standards it favours - those of the WHO or of a manufacturer could be considered equally valid.

- Increasing or partial privatisation of health care services with the implied many players bringing competition.

- If public health services exist, dilute the focus on it even as the State pays lip service on more investments in health.

- Where complete privatisation is not possible, advocate public-private partnerships.

- Emphasis on things like user fees in public health institutions and removing subsidies in health care, which further discourages the poor from using the health system.

- Move towards stronger patent, copyright and trademark regimes.

- Talk of global investments and global funds and newer vaccines for neglected diseases as if illness were prevalent only because of lack of investments and not because of lack of political will, lack of literacy, and unequal distribution of resources and food.

- Abdication by the State of its welfare roles with respect to the food, shelter, health and employment needs of the poor.

- And peculiar to India, talk of health tourism to earn foreign exchange (that is offer treatment to richer countries at much cheaper prices) whilst our own people go abegging for adequate health care services. Corporate hospital chains of India are opening up branches abroad and thanks to GATS the field is cleared for it in advance in the foreign country of any land mines.

More importantly the myth is propagated that the Market will take care of all inequalities and even routine governance issues of the State! The market would of course decide on the prices of health services and drugs and even the kind and quantity of drugs that would be made.[15]

Reality is however not so textbook neat; in fact it is messy, nasty and brutish. More trade benefits those who have resources to produce, after satisfying their own needs for survival. The box *Anatomy of Health Disaster* (in Chapter 2) is merely indicative of what happens in a country like India, in spite of the pharmaceutical industry being fairly advanced: India that is now suddenly targeted as a destination for billions of speculative investment dollars as well as a destination of specious "contract research" by international pharmaceutical majors. The health disaster described is in one of the Southern States of India Andhra Pradesh (AP). Its elected Chief Minister (since defeated at the hustings) liked to see himself as the CEO of AP Inc; relied on Mckinsey's advice to make AP prosperous by 2020; and invited and gave, the likes of Bill Gates, poor people's land practically free so that the State could bring in jobs for the middle-class at Microsoft's back

Key Health Concerns with WTO Agreements

Agreement	Health impacts from loss of
Agreement on Trade Related Intellectual	Limited access to essential medicines. Higher cost of drugs drains money useful for primary health care.
Agreement on Sanitary and Phytosanitary Measures	Requires scientific risk assessments even when foreign goods treated no differently than domestic goods (i.e. there is no discrimination). Such assessments are costly and imperfect with many health risks associated with environmental and manufactured products.
Technical Barriers to Trade Agreement	Requires that any regulatory barrier to the free flow of goods be as 'least trade restrictive as possible'. Many trade disputes over domestic health and safety regulations have invoked this agreement. To date only one dispute favoured the exception allowing countries to abrogate from rules to protect health (France's ban on the import of Canadian asbestos products).
Agreement on Trade Related Investment Measures	Limits countries' abilities to direct investment where it would do most good for domestic economic development and employment equity, both important to population health.
Agreement on Government Procurement	Limits government's abilities to use its contracts or purchases for domestic economic development, regional equity, employment equity or other social goals with strong links to better population health.
Agreement on Agriculture	Continuing export and producer subsidies by the USA, EU, Japan and Canada depress world prices and cost developing countries hundreds of millions of dollars in lost revenue which could fund health-promoting services. Subsidized food imports from wealthy countries undermine domestic growers' livelihoods. Market barriers to food products from developing countries persist and deny them trade-related earnings.
General Agreement on Trade in Services	Locks in and could increase private provision of key health-promoting services, reducing equitable access by poorer families and groups.

Source: Table reproduced with thanks from *Global Health Watch Report 2005-2006*

Source: David Werner, et al. *Questioning the Solution.*

Why does structural adjustment not slash military budget instead of health and education?

office in India.

The State saw (some will say how you can connect this and that) a spate of suicides of farmers mostly male leaving women and children to their fates. Part of the suicides was also related to failure of crops due to genetic seeds of a company called Monsanto but that is another story.

The mistake of giving primacy to the Market has been now acknowledged by the *Task Force on Child Health and Maternal Health* of the Jeffrey Sachs-chaired UN Millenium Project:[16]

> Even the most ardent health-sector reformers, however, recognize that market-based reforms based on the commodification of healthcare will end up failing to reach the poor, who simply do not have sufficient cash or other assets to purchase the care they need. They also recognize that such "market failure" means that a segment of the population will continue to suffer poor health…
>
> … Health sector reforms were expected to increase both efficiency (through markets) and equity (through the broader reach of an invigorated private sector for those who could pay and a 'residual' public sector for those who could not). That was the theory; the reality has been far different and, of course, rather varied as well. But, quite systematically, these reforms have been experienced as deeply unequalizing (Mackintosh 2001). Moreover, the theoretical neatness of discrete public and private sectors, each with its own role, pertains almost nowhere (Bloom and Standing 2001). People rich and poor face a pluralistic market with a wide and chaotic array of services of wildly varying quality that in virtually all cases require outlays of cash to access, even in the public sector where fee-exemption schemes are in place.
>
> The overall weakening of the state has left it unable to perform the regulatory and governance functions on which a market-based system depends (in many cases it was not strong enough to perform these functions well in the first place). That failure, and the chaos and inequity that result, intensify the problem: they further erode the state's legitimacy in the eyes of both the people who make up the health system and the people who look to it for managing health and disease quite often for matters of life and death.

The feeling of being excluded from health facilities and curative systems is the feeling of many poor people and women all over. Yes, some manage health care in dire circumstances but at a terrible cost to themselves. In India health care costs are the second largest cause of rural indebtedness and medicine costs account for 50 to 80 percent of health care costs. The costs of seeking health care will only become all the more unaffordable with TRIPS, WTO and the free market world views.

But is the market really free in health care services? That is the question we address next.

1.3 Does a Free Market Exist in Health Services and the Pharmaceutical Industry?[17]

We have already argued elsewhere in this book that perfect competition and a free market do not exist in reality in health services in general and in India's pharma industry in particular. Competition felt Adam Smith, and many after him, should reduce prices. What is competition? To an economist it means:

1. Existence of very large number of buyers and sellers, each consuming and producing a small fraction of

the goods in the market.

2. The producers and consumers are such a small fraction of the market that whether they buy or sell, it has no influence over supply and demand.
3. All the items in the market must be identical.
4. There can be no substantial barriers (obstacles) to entry into, or exit from, the market.

The overwhelming presence of a handful of pharmaceutical transnationals negate both condition (1) and (2). Also with the introduction of TRIPS and TRIPS plus, there are considerable entry barriers for any new entrant. Certainly this is no level playing field especially when I have built my company in the absence of such strict patent laws:

> Those who have challenged the inequalities of global trade have pointed to the fact that some of the world's richest nations once used tariff barriers to devastating effect in building their economies. But the history of patent protection suggests that that is not the only means by which the rich nations have raised the drawbridge after entering the castle. When it suits the rich countries to impose free trade, they do so. When it suits them to impose protectionism, they argue that this is the only path to development. But woe betide the poor nation which seeks to apply the lessons of the past.[18]

In economic literature, market failure is said to occur when inter alia (comments in italics ours):

1) Adequate competition does not exist.

   Entry barriers like TRIPS and product patents (with a possibility of evergreening for another 20 years) do not an adequate competition make.

2) Buyers and sellers are not well informed. Without information uneducated decisions are made.

   Certainly buyers are not informed. In fact medicines are the only area the consumer does not have a choice. The doctor makes the decision usually when the patient is in distress.[19]

3) Resources are not free to move from one industry to another (resource immobility).

   Mobility is not possible so easily given the scale of market at stake.

4) Prices do not reasonably reflect the costs of production.

   Enough has written about the overcharging and claiming of high selling prices due to high costs of discovery.[20]

5) Presence of

   * Negative externality - harmful side-effect that affects an uninvolved third party. In most events, it constitutes external cost.

     In this case, production of me-too drugs, 20-year long patents and data exclusivity provisions restricting entry of other players and use of unethical marketing techniques.[21]

   * Positive externality – beneficial side-effect that affects an uninvolved third party.

6) Production of public goods (supplementation by the government or subsidy).

   Most block buster drugs including AIDS drugs have been first developed in public funded institutions like NIH in US.

By all criteria we should regard the pharmaceutical industry, with IP rights, as a case of market failure. But as the old fox Adam Smith observed, "People of the same trade seldom meet together even for merriment and diversion, but the conversation ends in a conspiracy against the public or some contrivance to raise prices." In the case of India, agreeing not to freely produce the drugs that it needs, and passing legislation to ensure that, is a self-inflicted wound.

With profit and patents being the goals for pharma firms, companies tend to make what is profitable at the prices they perceive the market can take. Western pharma companies would cater to the kind of disease profiles and drugs that bring money in the developed countries. Drugs for problems that poor people and women in LDCs suffer are not priorities. One of the reasons, there has been such feverish international activity, among the very actors who sanction WTO and free trade, for setting up funds on drugs for neglected diseases and finding vaccines for diseases other than AIDS.

1.4 TRIPS Plus, Free Trade Agreements (FTAs) with the US and Access to Drugs[22]

Many developing countries, such as Kenya and Malawi, and some would say even India, have enacted stronger laws than the minimum required by TRIPS. Also many LDCs and developing countries have ended up signing free trade agreements with the US and/or EU. And many pharmaceutical majors are shooting on the shoulders of the pro-industry US Government through these bilateral "free trade agreements." (See box below *FTAs and the Art of Making Enemies.*)

As of writing, at least the following countries have signed free trade agreements with the USA: Morocco, Guatemala, Honduras, Nicaragua, Costa Rica, El Salvador, Dominican Republic (Central American Free Trade Agreement, CAFTA), Jordan, Singapore, Chile, Canada, Mexico (North American Free Trade Agreement, NAFTA), Australia.

The following countries have begun, or are due to begin, negotiations on trade agreements, which are likely to contain TRIPS plus provisions: Thailand, Bahrain, Panama, Bolivia, Colombia, Ecuador, Peru/Andean Community, Botswana, Lesotho, Namibia, South Africa and Swaziland, (Southern African Customs Union), Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, (South) Korea, Malaysia, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Christopher and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Thailand, Trinidad and Tobago, Uruguay, Venezuela (Free Trade Area of the Americas), Middle East Free Trade Area (to be concluded by 2013).

"These regional and bilateral trade agreements are the product of very unequal power relations. They are a deliberate effort to undermine the multilateral trading system. They are contrary to the values expressed in the 2001 WTO Doha Declaration on TRIPS and Public Health. Unless the WTO can place meaningful restraints on such trade negotiations, consumers, including poor consumers, will not be protected from the effects of excessive and inappropriate intellectual property rules."[23] These FTAs contain one or more of the following provisions to restrict the flexibilities, which had been wrangled at Doha:[24]

- Restrictions to the grounds for compulsory licensing
- Restrictions on parallel trade

- Controversial obligations to create exclusive rights to the test data used to register new drugs
- Extensions of patent terms beyond 20 years
- Obligations for drug regulators to enforce patents of dubious validity or relevance
- Obligations to grant patents on second uses of medicines.

The Center of Concern/International Gender and Trade Network[25] estimates that CAFTA's intellectual property (IP) rules limit compulsory licensing of CAFTA (Central American Free Trade Agreement) countries and prevent the marketing of a cheaper generic drug if a patented version already exists. This would have severe repercussions for the more than 200,000 Central Americans currently suffering from HIV/AIDS and lack the resources to pay for treatment.[26]

> As the primary providers of healthcare for their families and communities, women would bear increased burden under CAFTA's IP laws, as access to cheap drugs and medicines may become less available. One analysis conducted in Costa Rica revealed that IP measures outlined in CAFTA would increase the cost of some medicines by as much as 800%.[27]
>
> FTAs (Free Trade Agreements) actually instead of promoting free trade, they strengthen the stranglehold of big pharmaceutical over poorer countries and by selective provisions in the details of the agreements ("the devil is in the details") restrict the options of a poor country to reduce costs of medicines and health care .
>
> Under CAFTA's IP provisions, it will be difficult for poor people and indigenous communities to continue to use and protect traditional medicines and agroforestry and biodiversity systems. As the keepers of traditional knowledge, women often benefit from the sale of traditional handicrafts and use traditional medicines to safeguard the health of their families and communities. In Central America, women plant, transplant, and maintain trees, collect fruits, oils, and medicines from trees to use in the home or sell in local markets, and maintain subsistence farms and traditional agroforestry systems.[28]

With profit and patents being the goals for pharma firms, companies tend to make what is profitable at the prices they perceive the market can take. Western pharma companies would cater to the kind of disease profiles and drugs that bring money in the developed countries. Drugs for problems that poor people and women in LDCs suffer are not priorities. One of the reasons there has been such feverish international activity for setting up funds on drugs for neglected diseases and finding vaccines for diseases other than AIDS., from the very actors who sanction WTO and free trade.

1.5 Patents as Monopoly Devices

A patent is a means for creating and ensuring a monopoly. It has been shown that many a drug, which enjoys "block buster" status, is the result of initial development/discovery in a publicly funded research center or university.[30] So there is something akin to claiming too much of property rights than justified. When these so-called intellectual property rights conflict with health of nations, the tragedy and the absurdity are even starker.

Innovation and creativity flow from free creation of the human mind, and not in an atmosphere when one has to look over the shoulder all the time as to what property right or patent right one is violating. The great, fundamental discoveries of science have never been patented. Nor did Newton, Einstein, Francis Crick or

Alexander Fleming. And that is why we have been able to make such rapid progress in the twentieth century. At what point knowledge and technology derived from common property and common heritage of humankind becomes private intellectual property is indeed puzzling. Indeed Newton meant what he said, he was not being modest: "If I have seen further it is by standing on the shoulders of giants."

FTAs and the Art of Making Enemies

It would be nice if US citizens had more information about US foreign policy. If they did, they might understand why so many people hate us.

This week US trade officials are meeting with Thai negotiators in Chiang Mai, Thailand, to hammer out details of a still secret deal between the US and Thailand on what is inaccurately called a "Free Trade Agreement," or FTA …

… In Thailand, like everywhere else, the US government doesn't really negotiate the IP rules, it just announces the changes a country will have to make in its laws. The message is simple: no IP chapter = no "market access" agreement…

…The details of these policies can be complex, but they are all aimed at blocking generic competition and reducing the effectiveness of government negotiations over drug prices. One such measure would require generic drug companies to conduct their own clinic tests of the safety and efficacy of new drugs -- something that is time-consuming, costly and unethical. The US is also demanding extensions of pharmaceutical patent terms beyond 20 years, procedures that make it easier for foreign companies to obtain patents on medicines, and obligations for linking patents (even those of dubious validity or relevance) to drug registration. Some but not all of these measures are part of US law now.

In 2004, Thailand had a per capita income of $2,540, compared to $41,400 for the United States. With a per capita income that is 94 percent lower than the United States, it is not surprising that efforts to raise prices for medicine are not popular in Thailand ...

Maybe people in the US don't care what our government does in Thailand and other countries, and maybe if they did they would agree that raising drug prices worldwide is a good way to advertise our superior political and cultural values and maintain our high standard of living. But I doubt it.

If successful, the US proposals will kill people, and not for the first time …

…When you wonder why people hate the United States, think about the Thai FTA. Better yet, do something to stop our government from doing something that will cause so much lasting harm - to the Thai people, and to our honor.

- *James Love*, Consumer Protection on Technology[29]

1.6 TRIPS and WTO

Debate in India and elsewhere on WTO (World Trade Organization), patents and TRIPS (Trade Related Intellectual Property Measures) usually reflect at least three broad positions: a) WTO/TRIPs are part of a country's international commitments and obligations as we have signed an agreement in the comity of nations and therefore we should honor them faithfully. b) Let us make the best of a bad bargain that is WTO/TRIPS using the so-called flexibilities in TRIPS Agreement and Doha Declaration if need be. c) The TRIPS and WTO go against the fundamental grain of openness, creativity and what is at stake is the survival, welfare and development of all human beings and they need to be resisted.

Among the reasons for introduction of TRIPS has been the fear among MNCs that countries like India, Brazil, Argentina and China will sell drugs cheap and soon end up dominating the world market. Also somebody selling quality drugs at lower prices would rob the justification for MNCs pricing it high (or "as much as the market can take"). Big Pharma companies and Western Governments, chiefly the USA, introduced the notion of "intellectual" property rights in the guise of protecting the idea of free trade -

whereas in reality it was the mother of all trade barriers.

We are in distinguished company when we assert that the TRIPS Agreement is a barrier to free trade. The Columbia University economist Jagdish Bhagwati, considered by critics and admirers (and by himself), as the world's "foremost free trader", has this to say after arguing that MNCs do more good than harm:[31]

> Intellectual property does not belong in the WTO, since protecting it is simply a matter of royalty collection. But the matter was forced onto the WTO's agenda during the Uruguay Round by the pharmaceutical and software industries, even though this risked turning the WTO into a glorified collection agency. The move gave multilateral legitimacy to the use of trade sanctions to replace unilateral means of collecting royalties from developing countries, embodied in the tariff-retaliation provisions of the "special 301" legislation in the 1988 Omnibus Trade and Competitiveness Act. Tough restrictions were enacted under the TRIPS agreement on the manufacture of generic drugs and their sales to poor countries.
>
> During the period between the end of the Uruguay Round and the launching of the Doha Round, the pharmaceutical industry insisted that the TRIPS agreement was a done deal and should not be revisited (except to make intellectual-property protections tighter) -- even though virtually all trade rounds in the past have included renegotiation of issues that had been dealt with before. This game plan backfired, however, when the spread of AIDS in Africa and the widely recognized need for cheaper anti-retroviral drugs created huge pressure on the pharmaceutical industry during the few years preceding the Cancún meeting. The U.S. firms resisted this pressure for a long period. But finally, just prior to Cancún, the firms capitulated in the face of public opprobrium and handouts or threats from the Bush administration and agreed to accept a reduction of restrictions on the production and use of generic drugs. Thus, like the Singapore issues, the TRIPS problem was effectively avoided at the Cancún talks. And intellectual property largely remains off the agenda in Hong Kong, although some key details of a revised agreement (including protection for geographic brand names such as Burgundy wine, Parma ham, Roquefort cheese, and Darjeeling tea) remain to be worked out in a low-key fashion.

2. India, Patents and TRIPS

2.1 The 1970 Patents Act

The story starts with the 1970 Patents Ordinance. In fact even before that was the Patents Act of 1911 under the British Raj that provided for product patents for a period of 14 years. The 1911 Act itself was the result of several modifications starting from an 1856 Patents Act, modified subsequently in 1859, 1872, 1883 and 1888.

Most drugs in India in the pre-1970 era were expensive. Even the Kefauver Committee of the American Senate had observed that the prices of antibiotics and other medicines were the highest in India. About 85 percent of the medicines at the time were manufactured and/or marketed by MNCs. When we say a drug is/was expensive, we mean it is/was expensive for the middle class too. Even today many a drug, given poor price control, is expensive for a lower middle class person, not to speak of the wage labourer. And given irrational and unscientific prescription practices, corporatisation of health care and poor public health services in India, it often becomes expensive for the middle class too. But that is indicative of the even larger crisis in access to health services in India and deserves a separate discussion.

Post-Independence, the Government of India was keen on building the public sector and "attaining the commanding heights of the economy" in the pharmaceutical sector too. It was with this in mind the IDPL (Indian Drugs and Pharmaceuticals) was established. The Government in the meanwhile had realized that the 1911 Act really did not help the country and two high powered committees were appointed to examine the issue: the Bakshi Tek Chand Patent Enquiry Committee 1948-50 and the Justice Ayyangar Patents Revision Committee (1957-59). The 1970 Patents Act was an outcome of the recommendations of these Committees. The 1970 Patents Act was path-breaking both as a model patents act for developing countries and in the revolution it helped unleash in the pharma sector in India. (See box below on *Inventions not Patentable as per 1970 Patents Act*, that is before the April 2005 amendments.)

The 1970 Act did not allow product patents (readers may find it useful to have a look at the box below, *Definitions and Key Dates in TRIPS/IPR Related to Medicines*) in areas important for the country: in pharmaceuticals, food, insecticides, chemicals, etc. among others. In fact it specified only processes to be patented for "substances intended for use, or capable of being used, as food or as medicine or drug." (See box below for relevant extracts from the 1970 Patents Act). These patents for processes were to be for a maximum of seven years.

Inventions not Patentable as per 1970 Patents Act

(before April 2005 amendments)

3. What are not inventions

The following are not inventions within the meaning of this Act, -

a. an invention which is frivolous or which claims anything obvious contrary to well established natural laws;

b. an invention the primary or intended use of which would be contrary to law or morality or injurious to public health;

c. the mere discovery of a scientific principle or the formulation of an abstract theory;

d. the mere discovery of any new property of new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant;

e. a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance;

f. the mere arrangement or re-arrangement or duplication of known devices each functioning independently of one another in a known way;

g. a method or process of testing applicable during the process of manufacture for rendering the machine, apparatus or other equipment more efficient or for the improvement or restoration of the existing machine, apparatus or other equipment or for the improvement or control of manufacture;

h. a method of agriculture or horticulture;

i. any process for the medicinal, surgical, curative, prophylactic or other treatment of human beings or any process for a similar treatment of animals or plants to render them free of disease or to increase their economic value or that of their products.

4. Inventions relating to atomic energy not patentable

No patent shall be granted in respect of an invention relating to atomic energy falling within sub-section (1) of Section 20 of the Atomic Energy Act, 1962. (33 of 1962)

5. Inventions where only methods or processes of manufacture patentable

(1) In the case of inventions-

a. claiming substances intended for use, or capable of being used, as food or as medicine or drug, or

b. relating to substances prepared or produced by chemical processes (including alloys, optical glass, semi-conductors and inter-metallic compounds),

no patent shall be granted in respect of claims for the substances themselves, but claims for the methods or processes of manufacture shall be patentable….

Definitions and Key Dates in TRIPS/IPR Related to Medicines

Pre-1995 drugs (older drugs, including first-line ARVs)
TRIPS is not retroactive: drugs not patented in a WTO Member State before 1995 do not need to be patented by that Member State. However, these 'older' medicines may be on patent in developing countries that had adopted more restrictive national patent legislation before TRIPS.

1995-2005 'mailbox' drugs, TRIPS Article 70 (newer drugs including some second-line ARVs and cancer drugs)
WTO members which did not recognise patents on pharmaceutical products before 1995 were granted transition periods within which to become TRIPS-compliant. These countries, like India, were required to accept patent applications on post-1995 innovations and to hold them in a so-called "mailbox" for processing until that country became TRIPS compliant. Most developing countries started processing these in 2000, but countries such as India (which had legislation granting process patents, not product patents) were given until 2005 to become TRIPS compliant. In addition to holding the applications in a patent 'mailbox', transitional countries were required to grant patent applicants five years of exclusive marketing rights once the drug was in the mailbox and had been registered with the national drug regulatory authority, if that drug had also been patented and registered by another Member State. Least developed countries (LDCs) are exempted from accepting patent applications if they have passed legislation to extend their transition period until 2016.

2005 drugs (the newest drugs)
Except for LDCs, all WTO members must grant patent protection for pharmaceutical products as well as processes patented from 2005.

Transition periods for Least Developed Countries (LDCs) 2006-2016
Least developed countries must become TRIPS-compliant by 2006 unless they obtain further extensions. Transition periods for patents on medicines, however, were automatically extended until 2016 pursuant to Para 7 of the Doha Declaration, meaning that LDCs are not obligated by TRIPS to enact patent protections or to enforce existing patent rights until Jan 1 2016. Despite this new flexibility, national laws may still apply with respect to previously granted patents and thus even LDCs may need to issue compulsory licences or government-use orders with respect to previously granted patents.

Patent
A time-limited, territorially-based right to exclude others from making, using, offering for sale, selling or importing an invented product or from using an inventive process for 20 years after the patent is granted by a nation state (resulting in about 1015 years of market exclusivity). A country's patent law, and the specific patent status of a product, determine whether a drug's production, export and import are legal.

Exclusive marketing rights (EMRs)
A time-limited, territorially-based right to market a product without competition. Patents themselves grant a form of

EMRs, but EMRs may also be awarded to 'mailbox' patent applicants, in India for example, before a patent is granted so long as the medicine has been registered for distribution, assuming it has previously been patented and registered by another WTO Member State.

Drug Registration
Process by which drug regulatory authorities assess and confirm the safety, quality and efficacy of medicines in order to approve their use in the country. Innovator products, based on new chemical entities, require more complex assessment than their generic equivalents. Most countries therefore carry out a partial review based on approval provided by US or European Union regulatory agencies, the US Food and Drugs Administration (FDA) and the European Medicines Agency (EMEA). Assessment of generic drugs tends to take place at national level, where there is a comparable innovator product already in the market. However, access to, and the evaluation of, bioequivalence data can present a particular challenge for under-resourced national agencies.

TRIPS 1994
WTO Agreement on the Trade-Related Aspects of Intellectual Property Rights (1994) created an integrated framework for the protection of IPRs worldwide.

Doha Declaration 2001
Clarifies TRIPS flexibilities and asserts the primacy of public health and access to medicines for all.

Para 6 Decision August 30 2003
Permits non-producing countries to issue a compulsory licence to import medicines pursuant to a special compulsory licence for export issued in the exporting country. Countries include all LDCs and developing countries that can demonstrate insufficient capacity to manufacture a particular medicine. Widely viewed as a complex and unwieldy solution. Requires negotiation with patent holder for voluntary licence first (unless for government use etc as below), applies to a specific drug in needed quantities only, and product differentiation to reduce diversion. Both importing and exporting countries will need to pass enabling legislation.

Compulsory licence (including for government-use order, emergency based licence and licence based on competition grounds) (TRIPS Article 31)
Government authorisation permitting production of a patented product or use of a patented process (or importation by a non-producer) without the patent holder's consent. Issuance ordinarily requires prior negotiation with the patent holder for a voluntary licence, and payment of a royalty. An ordinary compulsory licence must be primarily for domestic use (over 51%), but could enable export of 49% to a nonproducer, without invoking Para 6 Decision (if an Article 31 ordinary compulsory licence is in place in the importing country). Licences issued to permit governmental, non-commercial use, or in order to address extreme urgencies or remedy anti-competitive practices, do not require prior negotiation.

A competition-based compulsory licence is not limited to the domestic market. A generic producer operating under a competition-based compulsory licence could produce unlimited quantities for export, including for LDCs with a legal extension to 2016, or a developing country with an ordinary compulsory licence or where there is no conflicting patent. Issuing such licences is a very complex process because of rights of appeal. The US has used anti-trust enforcement to limit market exclusivity of pharmaceutical companies, and required increased access to confidential data and manufacturing know-how.

Voluntary licence (TRIPS Article 40)
Agreement negotiated between patent holder and another company for manufacture and marketing. The regulation of anti-competitive features of voluntary licences is authorised by TRIPS Article 40. Regulation could favour export and regional production, non-exclusivity, technology transfer requirements, access to confidential test data access, and disclosure of reasonable royalty rates.

Parallel importation (TRIPS Article 6)
The importation of a patented medicine (at a cheaper price) where the patent holder's rights have been exhausted through the first sale (by the patent holder or licensee in another country). TRIPS permits countries to determine their own exhaustion regimes: international exhaustion permits parallel trade, and may permit importation of a drug produced under compulsory licence in another country. Pre-existing or new "TRIPS-plus" legislation often specifies national exhaustion. Here the patent holder has exclusive marketing rights, and resale is permitted only within the country after first sale. If no patent is on file, product can be parallel imported, irrespective of national legislation.

Discount or preferential pricing offers are frequently linked to the prevention of parallel importation between developing and developed markets (see EU anti-diversion regulation and recent ruling).

Limited exception (including Bolar exception) (TRIPS Article 30)
Limited and reasonable exceptions to patent holders' exclusive rights are permitted under Article 30, which could be justified if they do not conflict unreasonably with normal exploitation of the patent holder, taking legitimate third party interests into account. This could possibly be used to justify production for export and importation, using an ordinary compulsory licence or in the absence of a patent. The best known limited exception is the Bolar exception, which was first recognized in the US, and permits a generic company to formulate a generic product and to prepare its registration application before the patent expires. Data exclusivity rules (see below) may delay the date of final marketing approval if such approval is based on use of the innovator's registration data.

Data exclusivity (TRIPS Article 39) and TRIPS-plus sections of free trade agreements
In addition to protecting patent rights, TRIPS provides for protection of confidential drug registration data against unfair commercial use (for new chemical entities only). The US and Europe have legislated even greater data protections restricting access for 510 years to the confidential drug registration dossier submitted to secure regulatory approval for innovator drugs. This could prevent lawful registration of generics (because it prevents access to data for comparative assessment) and therefore can result in market exclusivity. The US in particular is seeking data exclusivity clauses in bilateral and regional free trade agreements.

[Reproduced in public interest from DFID publication *Under-served Markets: What are the implications of changes in intellectual property rights, trade and drug registration policy* available at
<http://www.dfidhealthrc.org/shared/publications/Issues_papers/ATM/DFID_synthesis_aw.pdf>]

2.2 Process Patents and Prices

As a result, the post-1970 period saw an explosion of manufacturing in formulations and APIs (active pharmaceutical ingredients or bulk drugs). Indian industry as of 2003 was supplying 20 percent of the world's drugs (by volume) and as of 2005 one of the largest pharma industry in the world (by volume). As of writing, at least 60 manufacturing plants in India have US FDA approval, second only to the United States itself. Most importantly, prices of medicines post-1970 tumbled. Pre-1970, India drug prices were one of the highest in the world. In 2004, India's drug prices are among the lowest in the world (dollar terms and even in purchasing power parity terms) with China as the possible exception for even lower prices.

The regime of process patents in drugs helped Indian industry reverse engineer/duplicate essential drugs and bring down the prices considerably. It also helped demystify the technology of production of APIs and formulations and showed how overpriced the prices of drugs were internationally in the name of recovering costs of R & D. It also helped demystify the technology of production of APIs (Active Pharmaceutical Ingredients) and formulations and showed how overpriced the prices of drugs were internationally in the name of recovering costs of R & D.

India became a signatory to the WTO/TRIPS Agreement in 1995. With it, India was given a 10-year transition period as a developing country, that is till January 1, 2005, to completely comply with WTO requirements. LDCs have transition period till 2016, that is, till 2016 they need not have a product patent regime.

The 1970 Patents Act was amended by the Government of India in 1994 by an Ordinance (which subsequently lapsed); then by a Bill introduced in 1999 and revised and passed in 2002; and finally again by the Third Amendment through a Presidential Ordinance on December 26, 2004. The last Ordinance was to be ratified by Parliament within 6 months for it to become an Act. Subsequently the Government of India, in an act of indecent hurry, passed the Patents Amendment Bill 2005 in the last week of March 2005 with the President giving assent to during the first week of April 2005. The April 2005 bill did try to accommodate some of the criticisms of the Dec 2004 Ordinance by health activists and people-oriented groups.

One needs to keep in perspective that product patents in the developed countries for medicines were introduced after having arrived at a position of strength. (See below *Patents and Bottomlines.*)

Patents and Bottomlines

... Almost all developed countries which are demanding product patents now had either a weak patent system or patents only for processes, especially for medicines. They introduced product patents in pharmaceuticals after their pharma industry was developed or needed to prevent other potential competitors.

Patents for products were introduced in Switzerland only in 1977. The law of September 4, 1967 introduced general patentability of chemical and pharmaceutical products in Germany. In France, In France, under the law of July 5, 1844 pharmaceutical inventions could not be patented and the ban on patenting drugs was completely lifted only in 1978. In Spain, the *Ley de Patentes* introduced patents for products in 1986, as a consequence of the country's entrance in the EEC. In Italy, pharmaceutical patents were prohibited until 1978, when the Supreme Court ruled in favor of eighteen pharmaceutical companies, all foreign, requesting the enforcement of foreign patents on medical products in Italy.

"... if patents were the source of medical innovation as claimed by intellectual monopoly apologists, the large historical and cross country variations in the patent protection of medical products should have had a dramatic impact on the pharmaceutical industries of the different countries. In particular, at least between 1850 and 1980, most drugs and medical products should have been invented and produced in the United States and the United Kingdom, and very little if anything in continental Europe. Further, countries such as Italy, Switzerland and, to a lesser extent, Germany, should have been the poor sick laggards of the pharmaceutical industry until the other day. Instead, as everyone knows since high school, the big time opposite is and has been true. This is as macroscopic a contradiction of the intellectual monopoly apologists' argument for patents in general, and for medical patents in particular, as one can possibly imagine."

(Quoted in *Against Intellectual Monopoly*, Michele Boldrin, and David K. Levine, online at <www.dklevine.com/general/intellectual/against.htm>, Nov 2005).

2.3 Reversing the Clock: Features of April 2005 Amendments to 1970 Indian Patents Act

How do the latest amendments of April 2005, and the earlier amendments, modify the original 1970 Patents Act of India? And how would they impact nationally and internationally the availability of generic medicines at low prices? We consider some of the major issues emerging with respect to medicines.

1) Protection for Product patents on drugs introduced for a period of 20 years. Generic versions in India of new drugs introduced internationally would have to wait for at least 20 years.

2) Mailbox facility for product patent applications introduced with provision of Exclusive Marketing Rights (EMRs) for the period Jan 1, 1995 to Jan 1, 2005. Fortunately, the April 2005 amendments clarify that there is no question of patent violation of drugs already in the public domain during this 10-year period. But a royalty may have to be paid as demanded by the patent holder. Other countries may import these and other drugs using parallel importation if necessary (agreed to under Doha Agreement).

3) Avenues for possible delays in issuing compulsory licenses appear to have been closed with the amendments specifying that the "reasonable" time period before the Patents Controller considers issuance of a compulsory license (CL) when such a license is denied by the patent holder "shall not ordinarily exceed six months." However, compulsory license procedures (see also box on FAQs below on Compulsory Licensing) could have been automatic in cases of diseases like AIDS and drugs for major problems like malaria, TB, diabetes, and for vaccines, etc. The Indian law provides for a number of grounds for the granting of such licenses on grounds of high prices, non-availability, to promote commercial activity, etc. "Refusal to deal" by the license holder could have also been included as a ground for issuing CLs. For the compulsory licensing system to be effective, procedures for granting such licenses need to be simple and effective. Terms of royalty have not been fixed nor a cap on royalty as such, leading to fears that this will further lead to price rise in the event of compulsory license being issued.

4) An earlier Dec 2004 Ordinance required that to export a patented product to an LDC, you not only need to have a compulsory license in India but also in the importing country. How a country with weak patent regulation or otherwise not required to give patent protection till 2016 shall make available a compulsory license to an Indian exporter was beyond understanding.

   This clause of the Dec 2004 ordinance had attracted widespread criticism (including famously and surprisingly in two editorials of the *New York Times*), as many developing countries would have been unable to import from India if this clause was retained. The April 2005 amendments now clarifies that the country can import from India if "by notification or otherwise allowed importation of the patented pharmaceutical product from India".

   The amendments have now provided that when patented drugs are produced under compulsory license in India by Indian companies: "*the license is granted with a predominant purpose of supply in the domestic market and that the licensee may also export the patented product, if need be in accordance with Section 84(7) (a) (iii)"* (i.e. where an export market exists). The amendments also add that a country can import from India if "by notification or otherwise allowed importation of the patented pharmaceutical product from India" that is no need for an importing LDC to issue its own overriding compulsory license. These provisions are not inconsistent with the latest Dec 2005 amendments in Hong Kong to the WTO TRIPS Agreement.

5) "Inventive step", "novelty" and "product" were less clearly defined in the earlier amendments leading to fear of evergreening of patents. Normatively, the definition of invention should be restricted to basic novel invention with all escape routes to evergreening closed.

The April 2005 amendments to the Ordinance tabled by the Government have now restricted the scope for the granting of Patents on frivolous claims. It clarifies that an "inventive step" means a feature of an invention that "involves technical advances as compared to the existing knowledge or having economic significance or both." The amendments contain a new definition for "new invention" by stating that it means "any invention or technology which has not been anticipated by publication in any document or used in the country or elsewhere in the world before the date of filing of patent application with complete specification, i.e. the subject matter has not fallen in public domain or that it does not form part of the state of art." The amendments also provide a definition for "pharmaceutical substance" as being "a new entity involving one or more inventive steps".

To minimize evergreening, the amendments clarify that "the mere discovery of a new form of a know substance which does not result in the enhancement of the known efficacy" is not patentable. It is further explained that: "Salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substances shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy". In addition the word "mere" has been deleted from the phrase "mere new use" in the Dec 2004 Ordinance under what is not patentable to strengthen the provision on denying Patents on the new use of a known substance. The phrase "unless they differ significantly in properties with regard to efficacy" has possibly left a door open for subjective interpretations.

6) Grounds for pre-grant opposition had been diluted in the Dec 2004 Ordinance. By reducing the number of grounds under which the grant of a Patent could be opposed from 9 to 2; it had also deleted the clause, which provided for a hearing in person to the person making the opposition. The new amendments of April 2005 have now restored all the original grounds in the previous Act for opposing grant of a Patent and has also provided that: "the Controller shall if requested by such person for being heard, hear him …" The time for filing such opposition has also been extended from three to six months.

7) In summary:
As per India's amended Patents Law, medicines patented before January 1, 1995 (irrespective of the date of launch by Indian companies) can be freely marketed without any arrangement with the innovator company irrespective of the expiry date of the patent.

Drugs patented subsequently up to January 1, 2005 (when the new Patent Law came into force) can be launched by manufacturers in India with approval from the innovators only.

If the drug has already been launched prior to January 1, 2005, the Indian manufacturer is required to make arrangements with the patent holder for continued manufacture and marketing. However no compensation can be claimed by the patent holder for the preceding period when the drug was being manufactured and sold without consent of the patent holder. What is important in Indian law is not the date of launch of a medicine or the expiry date of the molecule but the effective date of start of patent.[32]

However, the effectiveness of these amendments are to be seen only in the light of actual implementation.

Trading Up, CENTAD, Oct-Dec 05

Breaking the Ladder to Market Access

2.4 Not Taking Doha Agreement to the Fullest and other Issues

The Doha Agreement has clarified TRIPS flexibilities and clearly says that a country's public health needs can be given primacy above all. Unfortunately this interpretation has not been used either in the provisions of the recent amendments of India's Patents Act regarding more liberal grounds for compulsory license ("…each member has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted…") or for defining what drugs can and cannot be patented. Clearly the amendments to the1970 Act could have said that drugs of a certain therapeutic class important for certain crucial disease situations prevalent in India are out of patent.

Whether importation is to be considered as working of the patent? That is, does the patent holder need to manufacture the drug within India as proof of having worked the patent? The amendments are not clear on this aspect. Pending such clarity, there is no way the Government of India can control price of newly patented drugs even if it wants to as it would need data of costs of manufacture. Now the landed cost will have to be accepted as the cost. Patenting new essential drugs without an automatic procedure for compulsory license in case of overpricing, supplemented by India's ineffective price control regime, is guaranteed to make the situation worse.

The Government of India needed to amend only section 5 of the 1970 Patents Act to provide for product patents. Instead there are more than 70 amendments the Government of India has bent backward (this is what is meant by TRIPS Plus) and has not thought it fit to use the flexibilities afforded by TRIPS Agreement and the 2001 Doha declaration. Primacy has been given to concerns of MNC drug companies than the needs of the people of India. India is now a major source for good quality, low-priced APIs and formulations for many a third world country. This position will stand affected especially with respect to new drugs, which would enjoy a patent protection of 20 years, unless the Government of India would be willing to issue a compulsory license in the interests of public health. (See box below on FAQs regarding TRIPS and Compulsory Licensing.)

Can other LDCs still import from India overriding existing patents obligations to innovator companies? Yes they can at least till 2016 and afterwards by invoking CLs and by parallel imports if necessary. One should add provided they also have the political will to resist any apparently unrelated arm-tweaking. (See 2.5 below.)

TRIPS and Health: Frequently Asked Questions

Compulsory Licensing of Pharmaceuticals and TRIPS*

A certain amount of confusion exists about the TRIPS Agreement's provisions and compulsory licensing for medicines. These are some answers to questions that are frequently asked.

What is compulsory licensing?

Compulsory licensing is when a government allows someone else to produce the patented product or process without the consent of the patent owner. It is one of the flexibilities on patent protection included in the WTO's agreement on intellectual property, the TRIPS (Trade-Related Aspects of Intellectual Property Rights) Agreement.

Are these flexibilities new?

No. They always existed in the TRIPS Agreement, ever since it took effect in January 1995.

But what about the November 2001 Doha Ministerial Declaration on TRIPS and Public Health? Didn't that change the rules?

Not in general. Two provisions to do with **least-developed countries** and **countries that do not have production capacity** directly involved changes to the rules of the TRIPS Agreement. For the main part the declaration was important for clarifying the TRIPS Agreement's flexibilities and assuring governments that they can use the flexibilities, because some governments were unsure about how the flexibilities would be interpreted. Let's focus on the general case first.

OK. What is the general case?

For compulsory licensing, it's when the generic copy is produced mainly for the domestic market, not for export.

Is this the same as tearing up the patent?

No. The patent owner still has rights over the patent, including a right to be paid for the authorized copies of the products.

Does there have to be an emergency?

Not necessarily. This is a common misunderstanding. The TRIPS Agreement does not specifically list the reasons that might be used to justify compulsory licensing. However, the Doha Declaration on TRIPS and Public Health confirms that countries are free to determine the grounds for granting compulsory licences.

The TRIPS Agreement does list a number of conditions for issuing compulsory licences, in Article 31. In particular:

- normally the person or company applying for a licence has to have tried to negotiate a **voluntary licence** with the patent holder on reasonable commercial terms. Only if that fails can a compulsory licence be issued, and
- even when a compulsory licence has been issued, the patent owner has to receive payment; the TRIPS Agreement says "the right holder shall be paid adequate remuneration in the circumstances of each case, taking into account the economic value of the authorization", but it does not define "adequate remuneration" or "economic value".

There's more. Compulsory licensing must meet certain additional requirements: it cannot be given exclusively to licensees (e.g. the patent-holder can continue to produce), and it should be subject to legal review in the country.

* Source: <http://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm>, (Accessed Dec 14, 2005)

You said "normally"
Yes, this is where the confusion about emergencies arises. For "national emergencies", "other circumstances of extreme urgency" or "public non-commercial use" (or "government use") or anti-competitive practices, there is no need to try first for a voluntary licence. It's the only instance when the TRIPS Agreement specifically links emergencies to compulsory licensing: the purpose is to say that the first step of negotiating a voluntary licence can be bypassed in order to save time. But the patent owner still has to be paid.

Who decides whether the payment is "adequate"?
The authorities in the country concerned. The TRIPS Agreement says the patent owner must be *given the right to appeal in that country as well.*

And that's always been the case under the TRIPS Agreement? What has changed?
Yes, it's always been the case. What has changed is a provision that used to say that compulsory licences must be granted mainly to supply the domestic market (paragraph (f) of Article 31). The 2001 Doha Ministerial Conference decided that this should be changed so that countries unable to manufacture the pharmaceuticals could obtain cheaper copies elsewhere if necessary.

The legal means of making the change was agreed on 30 August 2003 when the General Council decided to waive the provision, allowing generic copies made under compulsory licences to be exported to countries that lack production capacity, provided certain conditions and procedures are followed.

All WTO member countries are eligible to import under this decision, but 23 developed countries are listed in the decision as announcing that they will not use the system to import: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Japan, Luxembourg, Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom and the US. Since they joined the EU, the list now includes 10 more: Czech Republic, Cyprus, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovak Republic and Slovenia.

As recorded in a separate statement that is not part of the waiver, 11 other members announced voluntarily that they would only use the system as importers in situations of national emergency or other circumstances of extreme urgency: Hong Kong China, Israel, Korea, Kuwait, Macao China, Mexico, Qatar, Singapore, Chinese Taipei, Turkey, and United Arab Emirates.

So all obstacles have been removed?
Not entirely. The WTO waiver on its own is not enough. To use the system, potential exporting countries probably have to change their laws too. This is where their laws complied with the original TRIPS provision by requiring production under compulsory licensing to be predominantly for the domestic market. So far Norway, Canada and India have informed WTO members (through the TRIPS Council) that their new laws and regulations are in place. The EU, Switzerland and Republic of Korea have said they are close to completing the legislation.

And least-developed countries?
They can now delay protecting pharmaceutical patents until 2016. So long as a medicine is not patented in a least-developed country, the government does not need to issue a compulsory licence to import. But the supplying country would have to issue a compulsory licence to export a generic copy of a medicine that is patented in that country.

Just to be clear, if a compulsory licence is issued it could be under the original TRIPS Agreement and not under the newer 2003 decision?
Correct. The 2003 decision (sometimes called the "Paragraph 6" decision because it refers to that that paragraph of the Doha declaration) only deals with compulsory licences to produce for export. Many news stories are about the possibility of issuing compulsory licences to supply domestic markets. That was always possible.

2.5 December 2005 Hong Kong Amendment

There were always flexibilities built into the original WTO TRIPS Agreement (for example Articles 8 and Articles 31[33]). WTO members were allowed always to issue Compulsory Licenses (CLs) under Article 31 of the WTO/TRIPS agreement on intellectual property. The November 14, 2001 Doha Declaration further clarified that "each Member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted"; and that "each Member has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency." The Doha Ministerial Conference also decided that this should be changed so that countries unable to manufacture the pharmaceuticals could obtain cheaper copies elsewhere if necessary.

The August 2003 Cancun meeting changed the provision that used to say that compulsory licences must be granted mainly to supply the domestic market (Article 31 f). But put in a lot of restrictions. The WTO meeting in Hong Kong made permanent these restrictions, of the Cancun meeting. In WTO legalese these are called "obligations" of exporting and importing members (see box below for exact language of these "obligations".).

An illustration of these obligations: a country wishing to import a generic version of a patented medicine would first have to notify the WTO of its exact needs regarding the patented medicine, and of its intent to issue a compulsory license in order to import it. Only after that could another country also issue a compulsory license to authorize the generic manufacture of the medicine for export. But the compulsory license issued by the first country would only be for the declared needs of one other country.

The amendment does not allow for the procurement of medicines through international tendering, which is the most common and efficient way of purchasing drugs. (See box above *A Sample of WTO Bureaucracy under the Hong Kong Amendment*, it is an indication of how cleverly worded apparently progressive amendments actually end up taking care of the IP protectionist lobbies of big Pharma.)

The drug-by-drug, country-by-country decision-making process, and the consequent, possible small quantities of the demand of the drug in the importing country may not induce manufacturers of an exporting country to take the trouble of getting a CL issued; and low prices of drugs may not result as there may not be the needed economies of scale. Ideally a company in India should have had the option of getting a CL issued by the government after due process, and had the freedom to export to a needy LDC without the intervention of the WTO as traffic police. Also, the possibility of many companies getting the CL and low prices of the drug (patented elsewhere) because of competition has become that much remoter.

Given such contexts, what are the other possible impacts, for the majority of the world's poor, of accession to WTO TRIPS? Some broad trends are discernible .

A Sample of WTO Bureaucracy made Permanent under the Hong Kong Amendment, Dec 2005

…the eligible importing Member(s)[i] *has made a notification to the Council for TRIPS, that: specifies the names and expected quantities of the product(s) needed;*[ii]

confirms that the eligible importing Member in question, other than a least-developed country Member, has established that it has insufficient or no manufacturing capacities in the pharmaceutical sector for the product(s) in question in one of the ways set out in the Appendix to this Annex; and

confirms that, where a pharmaceutical product is patented in its territory, it has granted or intends to grant a compulsory licence in accordance with Articles 31 and 31*bis* of this Agreement and the provisions of this Annex[iii]

the compulsory licence issued by the exporting Member under the system shall contain the following conditions:

only the amount necessary to meet the needs of the eligible importing Member(s) may be manufactured under the licence and the entirety of this production shall be exported to the Member(s) which has notified its needs to the Council for TRIPS;

products produced under the licence shall be clearly identified as being produced under the system through specific labelling or marking. Suppliers should distinguish such products through special packaging and/or special colouring/shaping of the products themselves, provided that such distinction is *feasible and does not have a significant impact on price; and*

before shipment begins, the licensee shall post on a website[iv] the following information:

the quantities being supplied to each destination as referred to in indent (i) above; and

the distinguishing features of the product(s) referred to in indent (ii) above;

the exporting Member shall notify[v] the Council for TRIPS of the grant of the licence, including the conditions attached to it.[vi] The information provided shall include the name and address of the licensee, the product(s) for which the licence has been granted, the quantity(ies) for which it has been granted, the country(ies) to which the product(s) is (are) to be supplied and the duration of the licence. The notification shall also indicate the address of the website referred to in subparagraph (b)(iii) above.

---

[i] Joint notifications providing the information required under this subparagraph may be made by the regional organizations referred to in paragraph 3 of Article 31*bis* on behalf of eligible importing Members using the system that are parties to them, with the agreement of those parties.

[ii] The notification will be made available publicly by the WTO Secretariat through a page on the WTO website dedicated to the system.

[iii] This subparagraph is without prejudice to Article 66.1 of this Agreement.

[iv] The licensee may use for this purpose its own website or, with the assistance of the WTO Secretariat, the page on the WTO website dedicated to the system.

[v] It is understood that this notification does not need to be approved by a WTO body in order to use the system.

[vi] The notification will be made available publicly by the WTO Secretariat through a page on the WTO website dedicated to the system.

Source: *Annex to the Protocol Amending the TRIPS Agreement, Article 31bis*. Italics ours; footnotes in the original. Complete text at <www.wto.org >.

3. Possible Impacts

3.1 Increasing Drug Resistance and Danger of Patent Gridlocks

A problem, which has complicated the control and treatment of infectious and communicable diseases, is the increasing problem of drug resistance in common infections and diseases of public health importance. Drug resistance has become increasingly frequent: chloroquine resistant falciparum malaria, multi-drug resistant tuberculosis TB (new strains resistant to both INH and rifampicin), in typhoid new strains resistant to not only to chloramphenicol but increasingly resistant to even quinolones is being seen, resulting in a dramatic escalation of cost, and requiring the use of 3rd generation cephalosporins. Deaths due to drug-resistant TB are the highest contributor to women's mortality in India.

Earlier acute respiratory infections were responsive to the effect of co-trimoxazole, which is an inexpensive drug. Now increasingly resistance to co-trimoxazole is being reported necessitating the use of other drugs for acute bacterial infections in children.

Urinary tract infections are one of the common causes of fever in women. E.Coli, which causes the majority of these infections, has also shown disturbing levels of resistance, first to co-trimoxazole, and now to quinolones and even cephalosporins.

Repeated and improper uses of antibiotics are primary causes of the increase in drug-resistant bacteria. Misuse of antibiotics endangers the usefulness of essential drugs. Decreasing inappropriate antibiotic use is the best way to control resistance.

One of the main reasons for improper use of antibiotics is poor access to competent medical advice leading to over/misprescription, illiteracy and pressures of daily hand-to-mouth existence; and of course, in many cases the nature of the disease itself. In addition, limited access to drugs, research on alternatives as much as flexibility to change from known therapeutic regimens to new ones, is hindered by the presence of trade barriers. (See box below, *Patent Gridlock?)*

Patent Gridlock?

…A June 1, 2005 report in a major AIDS journal (*JAIDS*) from a study of 306 patients in India found that of those treated over a year with one of two 3-drug regimens available, 46% had lipodystrophy [1]. The researchers also found that lipoatrophy was significantly associated with d4T use, and called for "improving access to alternative less-offending drugs like tenofovir and abacavir." This article ominously documents the development of a new global system of second-class medical care, imposed by trade laws that countries throughout the world have been pressured to accept….

…Multinational and Indian corporations are clearly aiming to sell new drugs to the richest 5% to 10%, meaning that 90% of the entire population of India will be denied access. Around the world, a substantial majority of all human beings may be disqualified from new drugs by patents and the resulting monopoly pricing. Financial inequality is so great that companies can make more money by selling to a small elite at prices that only it can pay, than by selling to everybody.

…Patent restrictions can block or greatly slow research and development of better treatments -- threatening the lives and health of everyone, even the richest, as no amount of money can quickly buy treatments and data that have never been created.

- John S. James in "Medical Innovation and Patient Gridlock" at <www.aidsnews.org>, June 2005

3.2 Increase in Prices and Decrease in Availability of Essential Drugs

Medicines prices are overpriced; drug companies in the US have claimed up to US $ 800 million as the cost of innovation of a new drug and therefore feel justified charging very high prices. We have discussed the hollowness of these claims in the Chapter on Pricing. Medicines in a monopoly market are usually priced at what the market can take. And cost of innovation of many drugs is often recovered in the first few weeks of sales in a developed country market. So why would a pharmaceutical company care to market in a developing country?

The product patent regime that the WTO/TRIPS mandate postpones the possibility of others with manufacturing capacity like India to bring down the cost of drugs. We have to wait for the product patent period to be over. Or if a country hopes to manufacture on its own before the 20-year patent lock-in period, it would need to issue a CL or Compulsory Licence. CL is a meaningful option only for countries with a manufacturing base in pharmaceutical APIs and formulations.

The TRIPS Agreement is however silent about the price control of patented products. But it is a moot point how many countries would dare use CLs or price control against the more powerful pharmaceutical companies. Price control again is an option only if it is manufactured within one's country then at least one could ask the manufacturer for price data.

A country could however use parallel import option, if one were available, that is import of the same drug from cheaper sources elsewhere. But this is only if a country, say an LDC, can negotiate (and has the capability) to negotiate a host of legal and administrative procedures; and provided a poor country has not tied itself with other binding agreements by signing a free trade agreement with the US or EU as discussed in Section 1 above.

One consequence is that public sector health service budgets are strained and dispensaries go without medicines for the major part of the year, one of the reasons people turn to the private sector in countries where both sectors exist. It also means that health systems of poorer countries transfer the scarce resources meant for treatment of life-threatening diseases to corporate shareholders.

For the majority of the poor in developing countries, the high drug prices means cutting back on other vital household expenses to pay for life-saving medicines. "When access to health care explicitly depends on the ability to mobilize cash resources, it effectively legitimizes exclusion of the poor."[34] (To get an idea of the lengths a corporate can go to protect its patent claims, at the expense of people, see the box below on *Terrorism, Pfizer Style*.)

3.3 Increase in Corporate Power: Against the Interests of Poor

The WTO/TRIPS regime reinforces corporate power as never before. Readers would be familiar with the story of how the cartel of big pharma in South Africa was broken by CIPLA, and thanks to the bold stand by the South African courts, when CIPLA came forward with AIDS medicines costing less than a dollar a day. Even as we write this, big pharma through the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) has "warned" that Brazil's decision to break a U.S.-held AIDS drug patent would turn foreign firms against cooperating with the country's health programs. This was in response to the Brazilian Health Ministry's intention to go ahead and issue a compulsory license order for the Kaletra antiretroviral (ARV) drug on the Sao Paulo office of Illinois-based Abbott Laboratories, the

Terrorism, Pfizer Style

- James Love

Pfizer is a big company. It has a market capitalization just over $183 billion, and a workforce of more than 100,000 persons around the world. Pfizer is also pretty aggressive.

Recently Pfizer sued the head of the drug regulatory agency in the Philippines, personally, asking for 1.4 million pesos in damages. Pfizer also sued another government official, the regulatory agency itself, and a government owned trading company.

Pfizer has also threatened Philippine news outlets, including television stations, with pull-outs of advertisements if they report on the dispute, and Pfizer has enlisted the US Department of State to pressure the Philippines government.

What is Pfizer up to? Well, they sell a drug, amlodipine besylate, that is marketed by Pfizer in the United States under the trade name Norvasc. It is used to treat hypertension, angina and myocardial ischemia. The drug is sold in two dosage formats: 5 mg. and 10 mg. tablets, and typically taken once a day.

In the Philippines, Pfizer charges from $.88 to $1.46 per day for Norvasc (more for the larger dose). In 2004, the average per capita income in the Philippines was $3.20 per day. Eighty percent of the population lives on less than $2 per day. Pfizer knows this. They have calculated that they can make greater profits selling Norvasc at a high price to a small number of the wealthiest Filipinos (less than 5 percent of the population can afford the drug), than a larger number of people with lower incomes

The Philippine government is trying to undertake some extremely modest measures to lower the price of this drug. They want to import versions of the drug that Pfizer sells in other countries. Pfizer charges much lower prices for the same drug in Thailand, Indonesia, India and other countries in the region. And, the Philippines government says it won't even do this until June 2007, when the Pfizer patent on Norvasc expires.

In other words, the Philippines government is allowing Pfizer to price Norvasc out of reach for 95 percent of the population of the country for the entire term of the patent, but they want the cheaper prices foreigners pay, when the patent expires.

But this isn't good enough for Pfizer. Pfizer is suing the government, and government officials personally, so it can stop the process of testing the imports. Pfizer figures this might delay the imports of the cheaper drugs for 18 months. And Pfizer also hopes they can stop the Philippines government from reducing the prices of other Pfizer products, including Lipitor, Zithromax and Unasyn, which are in a similar situation...

...Pfizer seems to be succeeding in bullying the Philippine government. Apparently the Philippine government has stopped efforts to register the cheaper imported products.

This is only the latest installment in a long history of pressure on the Philippines government. For example, check out this astonishing <http://www.cptech.org/ip/health/c/phil/philtimeline.html> report by Jennifer Ellen Mattson on a 1999 collaboration between the US government and pharmaceutical industry to oppose Philippine government effort to promote expanded use of generics for off- patented drugs.

It would be nice if the US news media would report on disputes like this, so US citizens would know what our government is up around the world (note the role of Clinton's Secretary of State Madeline Albright in the deplorable 1999 dispute), and it would be important also for the public to understand what type of company Pfizer is, and to appreciate why the Pfizer CEO Hank McKinnell is considered somewhat out of control even by other pharmaceutical company executives.

Source: <http://www.huffingtonpost.com/james-love/terrorism-pfizer-style_b_18290.html>

action was to slash the cost to its health budget of providing the drug free of charge to tens of thousands of AIDS sufferers. Abbott Labs had refused to negotiate a voluntary license, under which a Brazilian state-run laboratory would manufacture the drug and pay the company the actual cost of production. "A compulsory license order would send a strong signal to companies that Brazil does not welcome cooperation with pharmaceutical companies to address Brazil's public health needs", said Bale, a former US. trade negotiator and now part of the Geneva-based IFPMA. Please note the mafia-like use of the word "cooperation". Mr.Bale completely forgets that what Brazil is doing is perfectly within the ambit of flexibilities of the WTO.

If a country like Brazil can be subjected to these threats, the fate of smaller countries can be well imagined. Some of the latter have been forced into FTAs by the US government as was pointed out in Section 1 - which further restricts their freedom to use WTO flexibilities. Data exclusivity (see box below) and other restrictive clauses are being made mandatory by the US in bilateral agreements with smaller countries.

Data Exclusivity: Another Trade Barrier

The Government of India is currently (at the time we go to press) thinking of amending the Drugs and Cosmetics Act to introduce "data exclusivity": a provision that would preclude for a period of years both generic manufacturers and the Drug Controller from relying on clinical trial data submitted by an originator company to prove the safety and efficacy of the drug. Data exclusivity guarantees additional market protection for originator pharmaceuticals by preventing health authorities from accepting applications for generic medicines during the period of exclusivity. India's amended patent provisions are silent on data exclusivity.

Basically this would delay the entry of affordable generic equivalents in the market. And by requiring generic manufacturers to reinvent the wheel, the drug would become more costly defeating the idea of affordable generics.

MNCs are advancing a self-serving argument that once the country accepts patent, then "data accompanying patent information" is deemed to be accepted and hence exclusivity is also accepted. Legally it is not a valid argument. MNCs are now demanding that unless data exclusivity is ensured they would not conduct clinical trials in India.

However even TRIPS does not require this change: the Government of India thinks such a change is required under Article 39.3 of TRIPS. While all that is required is that clinical data relating to "new chemical entities" that require "substantial effort" in generating be protected from "unfair commercial use." There is no mention of any period of exclusivity.

Introducing data exclusivity would require intending generic manufacturers to conduct their own duplicate trials - a process guaranteed to add further costs. The immediate entry of competitors after exclusive rights end is essential in reducing the price of a product in the market.

In effect data exclusivity would delay and probably discourage new entrants - another form of trade barrier in a "free market" economy.

See also: 1) *Protection of Data Submitted for the Registration of Pharmaceuticals: Implementing the Standards of the TRIPS Agreement* by Carlos María Correa at <http://www.southcentre.org/publications/protection/protection.pdf>

2) Judit Rius Sanjuan. CPTech Discussion Paper No. 1. *US and EU Protection of Pharmaceutical Test Data*. at <http://www.cptech.org/publications/CPTechDPNo1TestData.pdf>

I don't have resources to set up such fancy laboratories to fulfill your standards
NO ENTRY
FIRST FULFILL STANDARD
0,000000000000

Trading Up, CENTAD, Oct-Dec 05

3.4 Mystification of Pharmaceutical Technology and Loss of Control

What the debate on TRIPS and access has done is it has mystified the technology of drug production for APIs (Active Pharmaceutical Ingredients) as well as formulations. In India, the mystification has to do with the obsession of making Indian industry world class and WHO GMP compliant, itself the result of WHO's attempts at harmonisation of quality standards, and such. While there are no complaints if a country produces quality drugs, many standards add to the cost of setting up a manufacturing unit, but even the process of trying to comply to these new norms has resulted in over 2000 small- and medium-scale Indian pharmaceutical industries closing down. Young entrepreneurs will think twice because of the prohibitive capital costs -- before starting a formulations industry or an API plant. The field by default (and some say design) is left to big players.

This is a tragedy of sorts as many of the big players in India today started as small-scale industries.

More importantly technology goes out of the hands of ordinary people and with it control over means of production. (See also box on next page: *Novartis Loses Patent Claim ...)*

3.5 Patenting of Traditional Medical Knowledge and Biodiversity

The patenting of indigenous knowledge and indigenous resources is a cause of great anguish for indigenous communities as well as developing countries from where biopiracy[35] is taking place. India has fought legal battles over Neem and Turmeric, which have been part of India's health and healing heritage. Patenting of Neem for biopesticidal properties which are known for centuries. Turmeric as anti-infective, bitter gourd (karela), Phyllanthus Niruri (for hepatitis) are few examples of biopiracy. Communities and groups who have been traditionally guardians of inherited wisdom of plant-based medicine are likely to be affected first by biopiracy and the commodification of biodiversity. Things that were in the public domain are being sought to be commercialised and be made inaccessible to common people.[36]

Novartis Loses Patent Claim on Cancer Drug: Patents Controller Upholds Natco Contention

- C.R. Sukumar

IN a major setback, the Swiss pharmaceutical giant Novartis AG has lost a patent claim for an anti-cancer drug Imatinib Mesylate before the office of the Indian Controller of Patents and Designs on Wednesday.

Following serious objections raised by Natco Pharma Ltd, a Hyderabad-based pharma company, the office of the Controller of Patents & Designs at Chennai has ruled against the claim of Novartis AG.

The patents office has refused to proceed further with the application for a patent filed by Novartis AG for Gleevec (Imatinib Mesylate), a life-saving drug used in the treatment of chronic myeloid leukaemia, sources told *Business Line.*

Novartis was earlier granted exclusive marketing rights (EMRs) in India for Gleevac. Natco Pharma, which launched a generic version of Gleevac under the brand 'Veenat', had challenged the grant of EMRs to Novartis. This case is currently pending before the Supreme Court.

Subsequently, Novartis had applied for an Indian patent and Natco had filed pre-grant opposition petition before the Controller of Patents & Designs, as provided in the amended Patents Act and Rules.

According to the judgment copy available … the patent application was rejected after due hearings on three grounds anticipation by prior publication, obviousness, priority and also on the ground that the product was a derivative of a known substance.

Natco has submitted to the Controller that Novartis AG has filed claim for a polymorphic form of Imatinib Mesylate. As per Section 3(d) of the Patents Act, any salt, polymorph or derivative of known substance is not patentable unless such salt, polymorph or other substance shows enhanced efficacy of the substance.

The Controller was informed that the specification states that wherever beta-crystals are used, the Imatinib free base or other salts can be used.

Further, Natco has submitted that the technical expert has conducted studies to compare the relative bioavailability of the free base with that of beta-crystal form of Imatinib Mesylate and has said that the difference in bioavailability is only 30 per cent and also the difference in bioavailability may be due to the difference in their solubility in water.

"The present patent specification (of Novartis AG) does not bring out any improvement in the efficacy of the beta-crystal form over the known substances rather it states the base can be used equally in the treatment of diseases or in the preparation of pharmacological agents wherever the beta-crystal is used.

"Even the affidavit submitted on behalf of the Applicant (Novartis AG) does not prove any significant enhancement of known efficacy," Natco submitted to the Controller.

Following this, the Assistant Controller of Patents & Designs, Mr V. Rengasamy, in his ruling on Wednesday said he was not convinced with the contentions of Novartis AG that the patent application claims a new substance. "It is only a new form of a known substance. It is found that this patent application claims only a new form of a known substance without having any significant improvement in efficacy."

Further, stating that Novartis AG failed to prove enhanced efficacy of the beta-isomer over the known substance, the Assistant Controller has concluded that, "the subject matter of this (patent) application (filed by Novartis AG) is not patentable under Section 3(d) of the Patents Act 1970 as amended by the Patents (Amendment) Act, 2005."

-*Business Line,* Jan 26, 2006

3.6 Deterring Research

Some form of reward system may be necessary to some persons and institutions involved in technical innovation. However if the reward system is restrictive and does not lead to diffusion of benefits of innovation to those who need it most, and in the case of pharmaceuticals, the poor and those afflicted, of what use is this paradigm of innovation and rewards? Business, trade and discovery is for overall human development, and not the other way around. Unfortunately the TRIPS/WTO thinking endorses the latter. One result is that corporate investments will go for diseases of the affluent rather than diseases afflicting the poor where there is less possibility of recovery of enormous profits.

To leave it to market forces to find a cure for AIDS or drug resistant TB is being too callous about our collective fate. A new paradigm for funding and doing research for public purposes is required.[37] Even without patents, fifteen percent of the world's population consumes 91% of the world's production of pharmaceuticals.[38] Industrial countries currently hold 97 per cent of all patents worldwide, while 80 per cent of patents granted in developing countries belong to residents of industrial countries.

Secondly, even for researchers, and those in pursuit of knowledge for knowledge's sake, does a restrictive patent system really promote free exploration of the human mind that advancement of knowledge needs? If one has to look over my shoulder, for all the time as to what patent or IP right I am violating, will one be able to do any good research? Innovation and truly fundamental paradigm shifts, novel and non-obvious, are likely to be snuffed out by fear of litigation. Indeed a system of competition and innovation where disputes are not settled by the true merit of an innovation but how good a lawyer one has, is indeed perverse and a sign of our collective greed.

As we point out in the Chapter on Pricing, many of the innovations and so-called blockbuster drugs had their origins in public funded institutions; so it looks like the ordinary public has to pay twice: once for the research through taxes, and again for buying the medicines at high prices through insurance or out of pocket payments.

> In the area of cancer, a study concluded that of the 37 cancer drugs developed since 1955, the US federal government was directly or significantly involved in the pre-clinical development of 18 drugs. In addition, it played some role in the pre-clinical research for 10 other drugs. In only nine of 37 cases was the National Cancer Institute (NCI) not involved at all in the pre-clinical research. When the drugs reached the stage for clinical research, NCI's role was even more pronounced. NCI played an important role in the funding of clinical research for 34 of the 37 drugs (Chabner and Shoemaker, 1989).[39]

It cannot be over stressed that many of the developing countries in the vanguard of advocacy for IP rights, themselves had IP protection in pharmaceuticals only after arriving at a certain stage of development. Now they seek to close the gates once they have arrived.

The social and human costs of patent dominated health care are likely to leave large sections of humanity worse off.

3.7 Market or the State: the Role of Medicine Price Regulation

The answer is obvious for some of us: the State clearly has a welfarist and interventionist role at the least in the areas of health, education and removal of hunger. With the (temporary?) collapse of the socialist state though not the ideology -- and the attempts at hegemonic sway by WTO and allied multilateral agencies, and the sole Superpower, one cannot wish away the market. One can hope to curb market fundamentalisms however, especially in so far as health and education and removal of hunger are concerned. If anything today the legitimacy of the State as an instrument of ensuring the right to health care and distributional justice needs to be asserted.

One area of contestation between free marketers and those seeking equitable distribution has been regulation and/or control of price of medicines. As discussed in the Chapter on pricing of drugs, India has had a fairly effective price control regime in place since 1978 (although it had, and continues to have, a large number of irrational and unscientific and hazardous medicines). Enthusiasts of opening up the economy in India would like to deregulate the pharma market completely especially with respect to price control. That is what the WTO/TRIPS protagonists want. But it does not serve the interests of very ordinary poor people as it makes the drugs even more unaffordable.[40] (See boxes below: *Patents and Welfare Loss* and *Another Example of how...*)

Not only pharma needs to be regulated as to its drug pricing, but also the kind of drugs it makes needs to be regulated. That certainly is the case for India. Pharma has to match its production to disease priorities and patterns prevalent.

Patents and Welfare Loss

A study by a World Bank economist and two Yale University economists estimates that in *the presence* of price regulation the total annual welfare losses to the Indian economy from the withdrawal of the four domestic product groups in the fluoroquinolone sub-segment *alone* would be on the order of Rs 20.16 billion. Out of which profit loss for Indian drug companies would be Rs. 2.3 billion. "…the loss incurred by producers - Rs. 2.3 billion on an annualized basis - pales in comparison to the decrease in consumer welfare … under the same scenario - Rs. 17.81 billion annually."

Source: *Estimating the Effects of Global Patent Protection in Pharmaceuticals: A Case Study of Quinolones in India.* Shubham Chaudhuri, The World Bank; Pinelopi K. Goldberg, Dept. of Economics, Yale, NBER and BREAD; and Panle Jia, Dept. of Economics, Yale, March 2006. Paper available at <http://www.econ.yale.edu/~pg87/TRIPS.pdf>

How Pharma Companies will be Pricing New Drugs in India

* A three-month course of Tarceva costs Rs 3,30,000.
* Only 3-5 per cent of India's 1,69,000 cancer patients can afford this drug.
* Roche has applied for a patent for Tarceva in India, but is uncertain about when it will come through.

Source: <http://www.ndtvprofit.com/homepage/storybusinessnew.asp?>, April 11, 2006

Trading Up, Apr-June 2005

4. What is to be done?

Several reports and Commissions[i] internationally have gone into the of the issues of intellectual property, patents and health., the latest of which is the WHO report[ii] *Public Health: Innovation and Intellectual Property Rights, Report of the Commission on Intellectual Property Rights, Innovation and Public Health*, April 2006. Being a WHO report it was a bit of compromise compared to the earlier report from UK's Commission on Intellectual Property Rights. Nevertheless the dissenting note of Carlos Correa and Pakdee Pothisiri summarises the issues at stake:[iii]

> As the report recognizes, patents are irrelevant for the development of the products needed to address the diseases prevailing in developing countries. Pharmaceutical companies decisively shape the global R&D agenda in this field and invest only where profitable markets exist. The extension of pharmaceutical patent protection to developing countries, mandated by the TRIPS Agreement, can do very little to prompt the development of such products, while it generates costs in terms of reduced access to the outputs of innovation. Where patents exist and are enforceable, medicines can be unaffordable for governments and patients in developing countries. This is why it is crucial to promote generics competition, which is essential to drive prices down and improve access to medicines to all, and to ensure a pro-competitive implementation of the TRIPS Agreement through the utilization, *inter alia*, of compulsory licences and government use provisions, when needed. Further analysis is required on the negative implications for public health of TRIPS-plus provisions (such as data exclusivity) contained in free trade agreements. WHO should continue to assess these developments and alert developing countries on their possible impact on public health.
>
> More analysis is also needed on the drastic decline in the capacity of the pharmaceutical industry to innovate, in spite of the availability of new powerful scientific and technological tools. Changes in the industry's structure, the focus on highly profitable products and a relaxation of the requirements of patentability, contribute to explain the industry's emphasis on the emulation or modification of existing products rather than on the development of genuinely new compounds. The report addresses but has not sufficiently elaborated on the profound distortions currently observed in the functioning of the patent system, which allows the proliferation of pharmaceutical patents on trivial developments that are used to obstruct generics competition.
>
> The coverage in the report of a broad set of issues ranging from discovery to delivery, which we personally did not favour, has led to the consideration of issues that are not central to the Commission's mandate and for which reliable evidence is limited. One case in point is companies' donation programs. Data on quantities, duration and other conditions of supplies, and the implications for the sustainable access to medicines need to be better examined in the appropriate context.
>
> We regret the Commission was not able to elaborate in more detail proposals for mobilizing the financial resources and the scientific talent, particularly that available in developing countries, necessary to address the diseases that predominantly affect the poor. This report will fulfill its objective, however, if it helps WHO member countries and other stakeholders to set R&D priorities and develop a global sustainable framework to respond to that imperative.

---

[i] *Integrating Intellectual Property Rights and Development Policy*. Report of the Commission on Intellectual Property Rights, London, November 2002. The full text of the report and the executive summary can be downloaded from the IPR Commission website: <http://www.iprcommission.org>. See box on the next page, *IP Rights: Skewed in Favour of Producers,* for an extract.

[ii] *Public Health: Innovation and Intellectual Property Rights*, Report of the Commission on Intellectual Property Rights, Innovation and Public Health, WHO, April 2006. For a select extract of some of its more useful recommendations, see Annexure 5.

[iii] *Public Health: Innovation and Intellectual Property Rights*, op.cit., Page 224.

IP Rights: Skewed in Favour of Producers?

…. It also needs to be considered what sort of rights IP protection confers. The conferring of IP rights is an instrument of public policy, which should be designed so that the benefit to society (for instance through the invention of a new drug or technology) outweighs the cost to society (for instance, the higher cost of a drug and the costs of administering the IP system). But the IP right is a private one, so the financial benefits and costs fall on different groups within society. The IP right is best viewed as one of the means by which nations and societies can help to promote the fulfilment of human economic and social rights. In particular, there are no circumstances in which the most fundamental human rights should be subordinated to the requirements of IP protection. IP rights are granted by states for limited times (at least in the case of patents and copyrights) whereas human rights are inalienable and universal. For the most part IP rights are nowadays generally treated as economic and commercial rights, as is the case in TRIPS, and are more often held by companies rather than individual inventors. But describing them as "rights" should not be allowed to conceal the very real dilemmas raised by their application in developing countries, where the extra costs they impose may be at the expense of the necessities of life for poor people.

We believe policy makers need to consider the available evidence, imperfect as it may be, before further extending IP rights. Too often, the interests of the "producer" dominate in the evolution of IP policy, and those of the ultimate consumer are either not heard or heeded. In IPR discussions between developed and developing countries, a similar imbalance exists. Developing countries negotiate from a position of relative weakness. The difficulty is that they are "second comers" in a world that has been shaped by the "first comers." The question is how they can mould their IP systems to suit their own economic, social, and technological conditions, as developed countries did in the past.

Intellectual property systems may, if we are not careful, introduce distortions that are detrimental to the interests of developing countries. Developed countries should pay more attention to reconciling their commercial self-interest with the need to reduce poverty in developing countries, which is in everyone's interest. Higher IP standards should not be pressed on developing countries without a serious and objective assessment of their impact on development and poor people. We need to ensure that the global IP system evolves so that the needs of developing countries are incorporated and, most importantly, so that it contributes to the reduction of poverty in developing countries by stimulating innovation and technology transfer relevant to them, while also making available the products of technology at the most competitive prices possible….

- Extract from Executive Summary of *Integrating Intellectual Property Rights and Development Policy. Report of the Commission on Intellectual Property Rights,* London, 2002.

Let us try and summarize the arguments advanced in this chapter.

TRIPS in WTO restricts access to drugs and will make new drugs costly. Patents, as Correa and Pothisiri note above, are "irrelevant for the development of the products needed to address the diseases prevailing in developing countries."

Supplementing this restrictive influence of patents are other instruments like GATS and Agreement on Technical Barriers to Trade (TBT) that restrict the shaping of health and other services in one's own country. The poor will be hit most by the liberalization and opening up of health services which the thinking underlying WTO/GATS advocates. Health problems of poor countries as much as of developed countries can be and have been solved only by active intervention of the State. Therefore you cannot leave medicine availability and health care access issues to the market. Commodification of health services through the principle of "let the market decide" will further completely exclude the poor, and among the poor, women more, from access to health services. Indeed opening up of markets needs more active intervention from the State in the form of good governance and checks and balance.

In this chapter, we have not even scratched the surface of the problems unleashed by TRIPS in seeds and agriculture on the poor and on women who are primary producers in 1/3rd of families heading the households the world over. TRIPS/WTO complicates the struggle for existence of ordinary women and poor. (The WTO agreement on Agriculture was drafted by Amstutz, a Cargill official, who led the US negotiations on agriculture during the Uruguay Round and is now in-charge of Food and Agriculture in the Iraqi Constitution - talk of revolving doors.)

TRIPS/WTO and pharma are part of the problem and not the solution. Indeed they make seeking solutions even more difficult. The following is a list of some of the steps needed apart from large doses of political will and commitment by governments to poor:

- Ideally the campaign to take TRIPS out of WTO must be continued. TRIPS has no place in WTO especially as related to pharma (and seeds and agriculture).
- Any opening up of health services under GATS must be studied for its adverse effects on health access to poor and women.
- Call for an end to free trade agreements that introduce TRIPS plus restrictive obligations on poorer countries that go against the spirit of Doha Agreement.
- In fact do not negotiate health in free trade agreements.
- Simplify issue of CL and parallel import for especially poorer countries. In principle, no country should issue patents on drugs for diseases that have a nation-wide impact on access to drugs for poor and women.
- Do not agree to data exclusivity clauses - TRIPS does not require it - or any other clauses that may make the manufacture of generics more difficult.
- See that governments increase, and not decrease investments in health services.
- Privatisation of health services, user fees, recovery of costs from poor, and other such conditionalities must be eliminated as part of World Bank/IMF loans.
- Countries must pass legislations that put microorganisms, plants and animals, traditional knowledge and biodiversity outside the purview of IP. And where women are the custodians of these traditional knowledge they must be adequately compensated in case the knowledge is commercialized.
- Governments must use price control mechanisms wherever possible to restrict high prices of medicines. These are within TRIPS flexibilities and as per Doha Agreement.
- Other important aspects of a rational, essential drug policy must be followed by all countries: restricting use and production to only essential and rational drugs.
- Develop the practice of regional nation blocs (example OAU, Latin American Countries, ASEAN, SAARC, etc.) to negotiate with pharma companies for patents, prices and technology.
- In the long-term, take medicines out of IP protection or give it as much protection as is in computers, software, planes and the like.
- Explore and develop the concept of open source status for medical and pharmaceutical technologies. Or special innovation funds for medicines for life-threatening diseases. If much of the world is dead, who will buy the medicines of the pharma companies?

Research in pharmaceuticals is needed, especially drugs for diseases that afflict the majority of the world's poor. How do we ensure such research and the fruits thereof are accessible to poor and women without having to look over the shoulder as to what patent rights is one violating?

There has been discussion among concerned persons on non-patent led drug discovery: (1) government-funded drug research (such as the CSIR in India and NIH in the US); (2) public-private partnerships driven by the needs and disease profile of India; (3) exploring and developing the idea of "open source" R & D in the emerging field of biotechnology; (4) the idea of a Patent Pool where individuals and groups develop drugs and put them in the public domain for a reasonable remuneration; (5) the proposed global biomedical R&D treaty which would permit each country to adopt its own form of R&D; (6) the institution of a prize fund for medical discoveries.

Other important strategies for manufacture of even existing out-of-patent medicines would include South-South technology transfer and trade collaboration in the matter of research, production and availability of medicines. Also it is important to resist the tendency of well-meaning professionals in WHO and international bodies to go overboard and mystify technology of drug production or even a relatively simple thing like formulations in the name of harmonization of standards. Such tendencies serve as trade and production barriers even as the need of the hour is demsytification of production technologies of pharmaceuticals.

The WTO is war by other means with trade and opening up as operative missiles - irrespective of the consequences. Globalisation in its present form is a losing game for many of the world's poor, and poor women much more: the economic might of international big pharma and big capital through the smokescreen of WTO plus threat from guns to those who dissent falsely labelled as clash of civilisations -- are the means of hegemony of the US/EU neo-liberal political elites; and one should add their accomplices among the Third World elites. The free market norms of WTO are tools to make the make countries 'safe' for foreign investors, at the expense of local communities' rights to determine their own futures. "WTO agreements undermine social and environmental policies, but protect the war industry through a "security exception" in the General Agreement on Tariffs and Trade (GATT) (Article XXI). The security exception states that a country cannot be stopped from taking any action it considers necessary to protect its essential security interests; actions "relating to the traffic in arms, ammunition and implements of war and such traffic in other goods and materials as is carried on directly for the purpose of supplying a military establishment (or) taken in time of war or other emergency in international relations."

As Michel Chossudovsky writes: "One cannot disarm the 'invisible fist' of the 'free market' without concurrently dismantling the military and intelligence apparatus that supports it. Military bases must be closed down, the war machine - including the production of advanced weapons systems - must be dismantled, implying a dramatic shift into civilian production."

Sure, health systems and drug related research and information have to be gender-sensitive and gender has to be "mainstreamed" but we need to realise peace will prevail only with the dismantling the military-WTO-free market complex. (See box on the page following: *"Life, Death and Drugs.")*

"Life, Death and Drugs"

.... Libraries have been written on the obvious connection between marketing and the lack of competition. The pharmaceutical industry is no exception to this rule, and the evidence Professor Sager, and many other, point at has a simple and clear explanation: because of generalized and ever extended patenting, pharmaceutical companies have grown accustomed to operate like monopolies. Monopolies innovate as little as possible and only when forced to; in general they rather spend time seeking rents via political protection while trying to sell at a high price their old refurbished products to the powerless consumers, via massive doses of advertising.

> *[Pharmaceutical] Companies today have found that the return on investment for legal tactics is a lot higher than the return on investment for R&D," says Sharon Levine, the associate executive director of the HMO Kaiser Permanente. "Consumers today are paying an inordinate premium under the guise of the creating the stream of innovation in the future. But it's actually funding lawyers."*

Economists call this "socially inefficient rent-seeking." It is ugly, but the polite academic jargon of "rent-seeking" means "corruption" and all that comes with it ...

... No, ladies and gentleman, the system is not functioning, and it cannot be otherwise, given the insane degree of monopoly and the complete lack of competitive discipline that pharmaceutical companies have become accustomed to. Yes, chances are that your medical doctor, the trusted counselor you see twice a year to make sure everything is all right, is getting gifts and promotional Caribbean vacations from a company that wants him to recommend their anti-depressive, not the other company's anti-depressive, even if both of them are useless. Anyone acquainted with the world of medical doctors has long known – often by listening to loud bragging at some cocktail party – that this is THE main marketing practice of large pharmaceuticals: buy out the doctors. Buy them with kickbacks, with paid vacations, with gifts, with phony symposia and conferences in expensive resorts where they are welcome to come "accompanied," with preposterous consulting jobs. The bill is on the consumer, or on the taxpayer, whichever comes first: it is the same person, in any case ...

...Whatever one feels about patents and the "property rights" of monopolists, it is hard to fathom the defense of existing patents when millions of lives are at stake. The current situation with respect to AIDS, or with respect to the possible "avian flu" pandemic reminds us of nothing so much as a scene from the movie Dr. Strangelove. The British Captain Mandrake must call the President of the United States with information that will save the world from destruction the only means of communication is a pay telephone, and neither he nor his escort Colonel Guano have any change. Mandrake spies a Coke machine in the corner and asks Guano to shoot it. To which Colonel Guano astutely replies "That's private property." The U.S. Navy during the First World War acted somewhat more creditably. When a dispute over patents between the Wright Brothers and Glenn Curtis threatened to derail airplane production, they simply ordered them to stop fighting or lose the patent.

Whatever religious altar one worships at, whether it be a more traditional religion, the religion of capitalism, or that of monopoly, there can be no excuse for allowing either the idea or reality of private property to interfere with the business of saving one's fellow man. If compensation for the taking of medical and pharmaceutical patents need be paid, so be it. But we can only hope that along with the great mass murderers of the 20th Century - the Stalins and the Hitlers - there is a special place in hell reserved for those who stood by and refused to act while those around them died.

Boldrin & Levine (2005): *Against Intellectual Monopo*ly, op.cit. Chapter 9.

Annexure1

TRIPS in WTO: Is it Logical?

The Columbia University economist Jagdish Bhagwati, considered by critics and admirers (and by himself), as the world's "foremost free trader", and also part of the WTO's executive board, has this to say after arguing that MNCs do more good than harm:[43]

> ... A prime example of such harmful lobbying by corporations in recent years has involved intellectual property protection (IPP). The damage inflicted on the WTO system and on the poor nations has been substantial. Let me explain.
>
> At the outset, the main issue here relates to the collection of royalties on patents and does not belong to the WTO, which is a trade institution. But pharmaceutical and software companies muscled their way into the WTO and turned it into a royalty collection agency simply because the WTO can apply trade sanctions. Getting IPP into the WTO means that these lobbies can use trade sanctions to collect the royalty payments they want!
>
> How did the IPP lobbies succeed? They first pressured the United States government to pass the so-called Special 301 legislation (in the 1988 Omnibus Trade and Competitive Act). Under this legislation, any country that did not extend IPP (as legislated by the United States) to U.S. companies, even though this obligation was not negotiated in any bilateral or multilateral treaty, was subjected to tariff retaliation for an "unreasonable" practice. Then NAFTA negotiations were used to get Mexico to drop its objections to IPP and to sign on to the IPP desired by the United States. U.S. lobbyists made it clear to Mexico that admission to NAFTA was conditional on this concession.
>
> With opposition by the developing countries being weakened by this use of punishments and inducements, the world trading system was being set up to accept IPP. In addition, pseudo intellectual justification was adduced by pretending that IPP was a trade subject: the magic words "trade-related" were added to turn IPP into TRIPS (trade related aspects of intellectual property rights). The U.S. trade representatives, first Carla Hills and then Mickey Kantor, promoted the propaganda (on behalf of the lobbying firms) that the poor countries would benefit from having to pay for patents they had been accessing freely until then!
>
> And since that sounded as implausible as the Mafia telling its victims that the protection money would keep them safe from arson, they also shifted the rationale to include the notions of "theft" and "piracy", implying that the matter was really one of rights to one's property. This changed rationale made little sense for two reasons. If I have a absolute right to what I have invented, this would be in perpetuity, when in fact the lobbying companies were merely arguing about lengthening the patent period. Then again, virtually all arguments made by economists use cost - benefit analysis, which means arguing for patents and their lengths in terms of whether they do good or harm a utilitarian form of analysis instead of a rights based approach.
>
> So with the conclusion of the Uruguay Round of multilateral trade negotiations and the establishment of the World Trade Organization in 1994, as astonishing capture of the WTO took place: TRIPS were introduced into the WTO integrally, as one of three legs of a tripod, the other two legs being the traditional GATT (for trade in goods) and the new GATS (General Agreement on Trade in Services). The latter two legs certainly belonged in a trade body. TRIPS, by contrast, were like the introduction of cancer cells into a healthy body. For virtually the first time, the corporate lobbies in pharmaceuticals and software had distorted and deformed an important

multilateral institution, turning it away from its trade mission and rationale and transforming it into a royalty collection agency.

Bhagwati goes on to lament that this is the reason why other lobbies found easy entry in WTO, namely pro-labor and pro-environment lobbies. That this happened so has been good, otherwise there would have been a danger of WTO becoming too one-sided.

Annexure2

Openness Promotes Growth?

It is not even clear not even to many of the World Bank experts who advocate these polices -- that openness in trade promotes growth!

> There is no empirical evidence that tariff cuts lead to growth. In effect, the Bank study accepts this, by saying (p 36) "Whether there is a causal connection from opening up trade to faster growth is not the issue."
>
> "Why not," asks Rodrik. If there be no claim of causal connection, why did the Bank invest so much of its intellectual capital on establishing the linkages between trade openness and growth?
>
> The real question is what kind of a policy conclusion could be drawn from this empirical evidence. In several of its earlier reports and studies, the Bank took the view, and advocated it, that a significant liberalization of trade is a key element in unleashing all the elements for growth and poverty reduction. "The latest report suggests that the Bank is not so sure, nor should any policy-maker in any developing country be," Rodrik comments.[44]

Annexure3

For Free Trade in Ideas

Economists Michele Boldrin and David K. Levine write in conclusion in their paper "The economics of ideas and intellectual property":[45]

> … Our own conclusion, based on empirical as well as theoretical considerations, is that on balance it would be best to eliminate patents and copyrights altogether. We have seen that markets for ideas are not so - turning it away from its trade mission and rationale and transforming it into a royalty collection agency.

> The government monopolies in Eastern Europe not only produced fewer and lower-quality goods at greater cost, but managed to do greater harm to the environment in the process. In developed economies, we have gradually replaced inefficient government grants of monopoly with more efficient mechanisms. Although many economists would not recommend eliminating patents and copyrights altogether, all recognize a strong need for reform. We suggest that insofar as it is desirable for the government to provide extra incentives for invention and creation, this is not best done through grants of monopoly, but rather through proven mechanisms such as subsidies, prizes, or monopoly regulated through mandatory licensing. Just as the world has used the World Trade Organization process to gradually harmonize a lower international level of tariffs, increasing greatly the benefits of the free market, so too it should be possible through international collaboration such as Trade-Related Aspects of Intellectual Property Rights (TRIPS) to harmonize substantial reductions in patent and copyright protection, greatly increasing the benefits of free trade in ideas.

Does Patent Protection lead to Innovation?

Even if one were to accept some kind of patent protection, it is not clear the kind of protectionism and monopoly rents sought to be imposed through TRIPS and WTO would promote innovation. The Brazilian expert Correa wrote:

> The TRIPS Agreement consolidates a new form of protectionism, which is not exercised through tariffs but through the appropriation of the knowledge used to produce goods and services. This highest expression of protectionism is, in the view of developed countries, a necessary condition to promote innovation and to stimulate technology and capital flows to developing countries. The assumption is that people from developed and developing countries will benefit alike from intellectual property rights.
>
> In the first place, the rationale of conferring monopoly rights over knowledge is in itself questionable. Knowledge can be used by everyone at once and, therefore; many may benefit from its use concurrently. It makes sense for society, as noted by Prof. Ned Hettinger ('Owning varieties of life: Historical, conceptual and ethical dimensions, Center for Biotechnology and Ethics, Texas A&M University', 1992), to grant exclusive rights to tangible objects because by its very nature the use by one person requires excluding others. But this is not the case of a "public good" like knowledge.
>
> Second, it remains unproven that a reinforced and expanded protection on intellectual property rights worldwide shall increase the flows of technology and capital to developing countries. On the contrary, UN studies ('Intellectual property rights and foreign direct investment', UN, 1993) suggest that innovatory companies in the North will increasingly opt, in the new post-Uruguay scenario, to directly sell the products or services that incorporate the innovations, rather than transferring the technology through foreign direct investments and licensing agreements.
>
> The likely result will be more exports by developed countries, and less opportunities for industrial and technological development for developing countries. A recent econometric study indicates, in this regard, a substantial increase in US exports to countries where intellectual property protection has been strengthened (Pamela Smith, 1995, "International patent protection and United States exports: evidence in the data", papers presented at international conference at American University).
>
> Third, it is in the logic of monopoly to charge as a high price as the market can bear, with the purpose of maximizing profits. Price increases, as discussed below, will be a regular feature, and not an accident, in the new regulatory framework.

Finally, increased profits neither necessarily means more private R&D[46], nor a lower contribution by the public to technological development. Prof. James Love (Presentation at ALIFAR International Conference, Bariloche, May 1994) has demonstrated that 12 out of 17 significant drugs developed in the United States between 1987 and 1991 were obtained with important government funding, and that these drugs were much more expensive (median cost of $4.854) than those developed without such funding (median cost of $ 1.626).[47]

Annexure4

Unfairness of Free Trade: WTO, a Neutral Arbiter?

Revolving Doors

What kinds of people and lobbyists are behind the WTO? What kind of revolving doors have been in operation? Let us see consider some examples:

Edmund Pratt, former CEO and Chairman Emeritus of Pfizer, attended numerous GATT negotiations as the official advisor to the US Trade Representative. He was a leader in the US private sector campaign to include Intellectual Property in the GATT Uruguay Round.

US appoints its candidate Paul Wolfowitz at the World Bank, the person who produced the intellectual arguments justifying the Iraq invasion and has shown little awareness of the challenges of development.

Pascal Lamy is appointed head of WTO. Lamy represented EU at the WTO for more than 5 years; Lamy pushed and bullied the WTO membership into launching a new round of trade talks even before the ink on the Uruguay round agreement was dry. Lamy argued for the WTO extending its remit to new and non-trade issues like foreign investment. And as EU trade commissioner, he strove to maintain its subsidy mountains and tariff walls in farm products. How can such a partisan public official who till recently was so aggressive about European interests now show neutrality and statesmanship at the WTO?

The outgoing WTO director general, Supachai Panitchpakdi of Thailand, on assuming office lost no time in going out of his way to accommodate the trade interests of the US and EU. Not surprisingly, Supachai is now going to walk across the street to head UNCTAD.

Peter Sutherland, who was instrumental in concluding the Uruguay GATT Round Negotiations and was Director-General of the WTO and GATT during1993-95, is now Co-Chairman of BP Amoco, Chairman and Managing Director of Goldman Sachs International, UK.

The late Arthur Dunkel, a former GATT Director-General, was a registered WTO dispute panelist, a board member of Nestlé and Chairman of the International Chamber of Commerce Commission on International Trade and Investment, which lobbied for an investment agreement in WTO.

"When I was the EU Commissioner responsible for trade negotiations I invited business leaders to become more involved. [...] Now that I am in the private sector myself, I am especially pleased to take on the Chairmanship of the high-level LOTIS Group." - Lord Brittan of Spennithorne.[48]

And some not so obviously connected but still:

> The connections between biotech companies and US regulatory agencies are deep. According to globalinfo.org, Ann Veneman, US Department of Agriculture Secretary, used to serve on the board of Calgene, the company that brought us the biotech tomato. She also used to head Agracetus, a subsidiary of Monsanto. In another example of the "revolving door" between biotech companies and regulatory agencies, the person who wrote the GMO regulations for the Food and Drug Administration (FDA) was a lawyer who "previously" represented biotech-giant Monsanto. After writing the FDA legislation, the lawyer returned to work for Monsanto.[49]
>
> In India, P.Chidambaram, the Finance Minister of India, an ardent WTO and free market advocate, was involved, after he became Minister, with a package resuscitating the failed Enron power project in India. Before he became Finance Minister he was the lawyer for Enron in its arbitration against the Government of India. Chidambaram also was counsel for many big pharma companies of India when NGO groups filed a case against the previous BJP government's Pharmaceutical Policy 2002.
>
> The drug industry itself played an active role in the last US elections.[50]
>
> "Economic heavyweights can easily get their voices heard within political arenas, because economic and political interests are always intertwined. Pfizer is said to be the most powerful political lobbyist of the pharmaceutical industry, and the drug giant is constantly using this power to make regulations, laws and policies suit its own profit-driven interest. E.g., Pfizer encouraged US politicians to threaten trade sanctions against poor countries producing or importing 'cheap' generic drugs, and the company pushed for a strict patent law within the World Trade Organisation."[51]

Removal of Subsidies, etc.: A Mere Sequencing Issue?

WTO is by its nature[52] host to big company pressures as well as to a more important and pernicious, if unstated, ideology namely that of the primacy of corporations and business over human and women's rights. Thus Intellectual Property Rights have been legitimised over and above the requirement of affordable medicines for the poor. Subsidies have been removed practically from India whereas the EU and US continue with farm subsidies and put barriers to textiles and garment exports.

Removal of subsidies is a contentious issue as it often means that suddenly your neigbourhood farmer or grocer is exposed to big traders and competition from outside, often outside the country.[53] And many simply perish in the process as they lack the wherewithal to reorient (or reinvent) themselves in the short run. Is free trade as a principle more important than lives of the people?

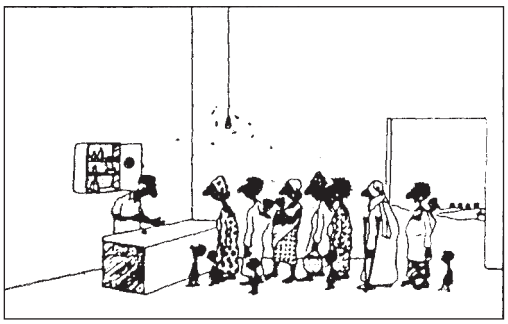
It is fashionable among economists, even some of the more sober ones, to view such questions as "major disagreements on the pace and sequencing of fiscal adjustment, monetary and interest rate policy, exchange rate regimes, trade and openness, internal and external financial liberalization including deregulation of capital flows, the scale and methods of large scale privatization of state owned enterprises, etc." even as seriously voiced concerns are damned as rhetoric, "Perhaps trade and openness is the archetypal, emblematic, area around which there are deep divisions, and where certainly the rhetoric is fiercest."[54]

> Typically economists from multilateral institutions, policy makers and protagonists of opening up the economy (say Group A) "tend to believe that the cause of poverty reduction is best served by more rapid adjustment to fiscal imbalances, rapid adjustment to lower inflation and external

deficits and the use of high interest rates to achieve these ends, internal and external financial sector liberalization, deregulation of capital controls, deep and rapid privatization of state owned enterprises and, perhaps the strongest unifying factor in this group - rapid and major opening up of an economy to trade and foreign direct investment. On each of these issues, group B types (international civil society, left of centre NGOs) tend to lean the other way.

The real question we face is why? Why is it that these two groups disagree so much across key areas of economic policy? … much of the reason lies in differences in perspective and framework on three key features characterizing assessments of economic policy, distribution and poverty: Aggregation, Time Horizon, and Market Structure. First, Group A tends to view the consequences of economic policy in much more aggregative terms than does Group B. Second, Group B's major concerns are with consequences over a time horizon which is both much shorter and much longer than the "medium term " horizon which Group A typically adopts. Third, Group A instinctively approaches the distributional consequences of economic policy through a competitive market structure, while Group B instinctively thinks of a world in which market structure is characterized by pockets of market power, and economic policy feeds through this non-competitive structure to the consequences for the poor.[55]

The underlying message even among so-called sympathetic economists is but for questions of aggregation and time horizon, the poor and the rich, the people laughing their way the bank (s?) and the ones at the receiving end, would all feel the same way about the new policies. Nothing can be farther from the truth apart from the fact that in the long run we are all dead. You just cannot have democratic pretensions and tell a poor person that economic theory says that opening up of the economy and WTO are good for you and the country and it will bring overall prosperity and in the end we would all benefit, and therefore please postpone your short-term misery coming out of me demolishing your home, or causing a few years of unemployment and hunger.



Annexure5

Some of the Useful Recommendations in the CIPIH Report*

page 70
2.10 Countries should provide in their legislation powers to use compulsory licensing, in accordance with the TRIPS agreement, where this power might be useful as one of the means available to promote, inter alia, research that is directly relevant to the specific health problems of developing countries.

page 74
2.12 Public research institutions and universities in developed countries should seriously consider initiatives designed to ensure that access to R&D outputs relevant to the health concerns of developing countries and to products derived there from, are facilitated through appropriate licensing policies and practices.

page 95
3.3 WHO should initiate a process to devise mechanisms that ensure the sustainability and effectiveness of public-private partnerships by attracting new donors, both from governments and the private sector, and also to promote wider participation of research institutions from developing countries. However, governments cannot passively rely on what these partnerships could eventually deliver; there is a need for a stronger commitment on their part for an articulated and sustainable effort to address the research gaps identified in this report.

page 106
3.5 Governments should continue to develop forms of advance purchase schemes which may contribute to moving later stage vaccines, medicines and diagnostics as quickly as possible through development to delivery.

page 107
3.6 Recognizing the need for an international mechanism to increase global coordination and funding of medical R&D, the sponsors of the medical R&D treaty proposal should undertake further work to develop these ideas so that governments and policy-makers may make an informed decision.

3.7 Practical initiatives that would motivate more scientists to contribute to this field through open source methods should be supported.

page 126
4.5 Policies for biomedical innovation must take account of the fact that health systems in many developing countries remain resource- constrained. Policies must emphasize affordable innovations adapted to the realities of healthcare delivery in developing countries, and covering appropriate technologies for the diagnosis, prevention and treatment of both communicable and noncommunicable diseases. Mechanisms for promoting such adaptive research in a systematic way must be improved.

page 133
4.6 All companies should adopt transparent and consistent pricing policies, and should work towards reducing prices on a more consistent basis for low and lower middle income developing countries. Products, whether originator's or generic, should be priced equitably, not just in sub-Saharan Africa and least developed countries, but also in low and lower middle income countries where there are a vast number of poor patients.

---

* WHO: *Public Health: Innovation and Intellectual Property Rights, Report of the Commission on Intellectual Property Rights, Innovation and Public Health,* April 2006, op.cit.

4.7 For noncommunicable diseases, governments and companies should consider how treatments, which are widely available in developed countries, can be made more accessible for patients in developing countries.

4.8 Continuing consideration needs to be given to the prices of treatments for communicable diseases, particularly of second-line drugs for HIV/AIDS treatment.

4.9 Governments of low and middle income countries where there are both rich and poor patients should formulate their funding and price regulation with a view to providing access to poor people.

4.10 Governments need to prioritize health care in their national agendas and, given the leverage to determine prices that patents confer, should adopt measures to promote competition and ensure that pricing of medicines is consistent with their public health policies. Access to drugs cannot depend on the decisions of private companies but is also a government responsibility.

4.11 Corporate donation programmes can be of great value in a number of fields in collaboration with the actions of governments and non-governmental organizations. However, addressing health needs in developing countries requires more structured and sustainable actions by governments and other parties to stimulate accessibility to products, while generating new treatments and products adapted to the needs of developing countries.

4.12 Governments should remove any tariffs and taxes on health-care products, where appropriate, in the context of policies to enhance access to medicines. They should also monitor carefully the supply and distribution chain to minimize costs that could adversely influence the prices of medicines.

page 139
4.13 The Doha Declaration clarifies the right of governments to use compulsory licensing as a means of resolving tensions that may arise between public health and intellectual property, and to determine the grounds for using it. Developing countries should provide in their legislation for the use of compulsory licensing provisions, consistent with the TRIPS agreement, as one means to facilitate access to cheaper medicines through import or local production.

4.14 Developed countries, and other countries, with manufacturing and export capacity should take the necessary legislative steps to allow compulsory licensing for export consistent with the TRIPS agreement.

4.15 The WTO decision agreed on 30 August 2003, for countries with inadequate manufacturing capacity, has not yet been used by any importing country. Its effectiveness needs to be kept under review and appropriate changes considered to achieve a workable solution, if necessary.

page 140
4.16 Companies should adopt patent and enforcement policies that facilitate greater access to medicines needed in developing countries. In low income countries, they should avoid filing patents, or enforcing them in ways that might inhibit access. Companies are also encouraged to grant voluntary licences in developing countries, where this will facilitate greater access to medicines, in cases where patents do exist on medicines and other products, and to accompany this with technology transfer activities.

4.17 Developing country governments should make available full and reliable information on patents granted. WHO, in cooperation with WIPO and others, should continue to pursue the establishment of a database of information about patents, in order to remove potential barriers to availability and access resulting from uncertainty about the patent status in a country of a given product.

page 141
4.18 Developed countries and the WTO should take action to ensure compliance with the provisions of Article 66.2 of the TRIPS agreement, and to operationalize the transfer of technology for pharmaceutical production in accordance

with paragraph 7 of the Doha Declaration on the TRIPS Agreement and Public Health.

page 142
4.19 The restriction of parallel imports by developed countries is likely to be beneficial for affordability in developing countries. Developing countries should retain the possibilities to benefit from differential pricing, and the ability to seek and parallel import lower priced medicines.

4.20 Developing countries need to decide in the light of their own circumstances, what provisions, consistent with the TRIPS agreement, would benefit public health, weighing the positive effects against the negative effects. A public health justification should be required for data protection rules going beyond what is required by the TRIPS agreement. There is unlikely to be such a justification in markets with a limited ability to pay and little innovative capacity. Thus, developing countries should not impose restrictions for the use of or reliance on such data in ways that would exclude fair competition or impede the use of flexibilities built into TRIPS.

page 145
4.21 In bilateral trade negotiations, it is important that governments ensure that ministries of health be properly represented in the negotiation, and that the provisions in the texts respect the principles of the Doha Declaration. Partners should consider carefully any trade-offs they may make in negotiation. Bilateral trade agreements should not seek to incorporate TRIPS-plus protection in ways that may reduce access to medicines in developing countries.

page 146
4.22 Governments and concerned international organizations should promote new purchasing mechanisms to stimulate the supply of affordable new products and to enhance the number of suppliers in order to provide a more competitive environment.

page 147
4.23 Developing countries should adopt or effectively implement competition policies and apply the pro-competitive measures allowed under the TRIPS agreement in order to prevent or remedy anti- competitive practices related to the use of medicinal patents.

page 148
4.24 Countries should provide in national legislation for measures to encourage generic entry on patent expiry, such as the "early working" exception, and more generally policies that support greater competition between generics, whether branded or not, as an effective way to enhance access by improving affordability. Restrictions should not be placed on the use of generic names.

4.25 Developing countries should adopt or effectively implement competition policies in order to prevent or remedy anti-competitive practices related to the use of medicinal patents, including the use of pro-competitive measures available under intellectual property law.

4.26 Bilateral trade agreements should not seek to incorporate TRIPS- plus protection in ways that may reduce access to medicines in developing countries.

page 152
4.27 Governments should take action to avoid barriers to legitimate competition by considering developing guidelines for patent examiners on how properly to implement patentability criteria and, if appropriate, consider changes to national patent legislation.

page 170
5.2 The formation of effective networks, nationally and internationally, between institutions in developing countries and developed countries, both formal and informal, is an important element in building innovative capacity. Developed

and developing countries should seek to intensify collaborations which will help build capacity in developing countries.

5.3 WHO, WIPO and other concerned organizations should work together to strengthen education and training on the management of intellectual property in the biomedical field, fully taking into account the needs of recipient countries and their public health policies.

page 174
5.4 Developed countries, and pharmaceutical companies (including generic producers), should take measures to promote the transfer of technology and local production of pharmaceuticals in developing countries, wherever this makes economic sense and promotes the availability, accessibility, affordability and security of supply of needed products.

5.5 Developed countries should comply with their obligations under article 66.2 of the TRIPS Agreement and paragraph 7 of the Doha Declaration.

page 177
5.6 Developing countries need to assign a higher priority to improving the regulation of medical products. Developed countries, and their regulatory institutions, should provide greater financial and technical assistance to help attain the minimum set of regulatory standards needed to ensure that good quality products are available for use. This assistance should also support infrastructure developments within a country, to ensure that good manufacturing practice and supply chain management standards are implemented and sustained.

5.7 The process of the International Conference on Harmonisation currently lacks immediate relevance to the needs of many developing countries, but those countries should maintain their participation in the process. In the meantime, developing country governments and regulatory institutions should give support to regional initiatives, tailored to the current capacities of their member countries, which offer more scope for lifting standards over time, exploiting comparative advantages, avoiding duplication, sharing information and facilities, and promoting appropriate standardization without erecting barriers to competition.

5.8 WHO has an important role to play, in collaboration with interested parties, in helping to strengthen the clinical trials and regulatory infrastructure in developing countries, in particular in sub-Saharan Africa, including the improvement of ethical review standards.

5.9 Apart from the European and Developing Countries Clinical Trial Partnership, donors together with medical research councils, foundations and nongovernmental organizations, need to offer more help to developing countries in strengthening clinical trials and regulatory infrastructure.

page 187
5.10 Digital libraries of traditional medical knowledge should be incorporated into the minimum search documentation lists of patent offices to ensure that the data contained within them will be considered during the processing of patent applications. Holders of the traditional knowledge should play a crucial role in deciding whether such knowledge is included in any databases and should also benefit from any commercial exploitation of the information.

5.11 All countries should consider how best to fulfil the objectives of the Convention on Biological Diversity. This could be, for instance, through the establishment of appropriate national regimes for prospecting for genetic resources and for their subsequent utilization and commercialization; contractual agreements; the disclosure of information in the patent application of the geographical source of genetic resources from which the invention is derived and other means.

Endnotes

[1] Vinay Lal. "Home Truths and McData". *The Little Magazine*. Vol V: Issue 4 & 5, 2004

[2] International NGO Solidarity Statement: US-Thai Free Trade Negotiations Threaten Access to Medicines; Activists Demand Suspension of Negotiations and End to TRIPS-plus IP Provisions, Jan 9, 2006. Full text available at <http://www.cptech.org/ip/health/c/thailand/solidaritystatement01092006.doc>.

[3] Typically these arguments try to show that the cake is greatly enlarged because of free trade and therefore presumably the divisions thereof; the real question is the fair and equitable division of the cake. Here is Amartya Sen on the theme of justice in a globalising world in an Address to the General Assembly of the UN on Oct 29, 2004: "… People from very deprived countries clamour for the fruits of modern technology (such as the use of newly invented medicines, for example for treating AIDS); they seek greater access to the markets in the richer countries for a wide variety of commodities, from sugar to textiles; and they want more voice and attention from the rest of the world. If there is scepticism of the results of globalization, it is not because suffering humanity wants to withdraw into its shell.

In fact the pre-eminent practical issues include the possibility of making good use of the remarkable benefits of economic connections, technological progress and political opportunity in a way that pays adequate attention to the interests of the deprived and the underdog. That is, I would argue the constructive question that emerges from the anti-globalization movements. It is, ultimately, not a question of rubbishing global economic relations, but of making the benefits of globalization more fairly distributed.

[4] These statements may appear telegraphic to the reader but there is a lot of literature, academic, semi-academic and activist advocacy organizations, on which these assertions are based some of these are referred/cited below.

[5] See Utsa Patnaik. "The Cost of Free Trade : The WTO Regime and the Indian Economy." *Social Scientist*, V.27: No.11-12 November-December 1999 #318-319.

[6] See also Jayati Ghosh "Economists and 'free trade' ", *Frontline*," Volume 22 - Issue 25, Nov. 05 - 18, 2005. Ghosh argues that "Imperialism has used controlled trade or supposedly free trade to suit its needs. The tragedy is that it has always been able to find economists who will willingly justify the chosen strategy of the moment."

[7] Bhagwati, Jagdish. "From Seattle to Hong Kong." *Foreign Affairs*, December 2005, WTO Special Edition. See also Annexure 1. Bhagwati has however very little sympathy with civil society groups for spoiling the party of high-minded tradewallahs at Seattle and now Hong Kong and would probably blanch at being quoted in this tract. He is to be viewed essentially as an academic-scholar-contrarian voice among free traders.

[8] See Annexure 2 for comments of economists Rodrik and Fingers who have advised the World Bank at one time or the other as full time consultants.

[9] For detailed discussion see, see for instance: *The Truth About the Drug Companies: How they deceive us and what to do about it.* Marcia Angell. Random House, 2004. Also see the chapter on pricing in this book (of LOCOST) and references cited therein.

[10] 1) See Michele Boldrin and David K. Levine "Perfectly Competitive Innovation," a report published by the Federal Reserve Bank of Minneapolis. The authors, who are economists, argue that copyrights, patents, and similar government-granted rights serve only to reinforce monopoly control, with its attendant damages of inefficiently high prices, low quantities, and stifled future innovation. More to the point, they argue, economic theory shows that perfectly competitive markets are entirely capable of rewarding (and thereby stimulating) innovation, making copyrights and patents superfluous and wasteful. Available at <http://levine.sscnet.ucla.edu/papers/pci23.pdf>. See also Annexure 3 for conclusions of their paper "The economics of ideas and intellectual property" in *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*, January 25, 2005, vol. 102, no. 4.

2) For a layperson's version of the above arguments, see "Creation Myths: Does innovation require intellectual property rights?" by Douglas Clement in *Reasononline: Freeminds and Free markets* at <http://www.reason.com/0303/fe.dc.creation.shtml>.

3) See also "Innovation-or-Patent-Colonialism"

at <http://www.iosn.net/foss/no-software-patents/news/innovation-or-patent-colonialism>, report of the Second Open Source Business Conference (OSBC).

4) See "Intellectual-property rights and wrongs" by Joseph E. Stiglitz in *Daily Times (Pakistan)*, August 17, 2005 at <http://www.dailytimes.com.pk/default.asp?page=3Dstory_16-8-2005_pg5_12>.

5) See also Correa on this, Annexure 3.

[11] Phrase courtesy P. Sainath's "McMedia & Market *jihad",* P.Sainath in *The Hindu*, June 1, 2004. See also Sainath's "And then there was the Market", *Seminar*, Jan 2001.

[12] Term originally coined by John Williamson in 1990, the consensus included reforms that should be undertaken from 1989 (these reforms were also summarized by the World Bank in its year 2000 Poverty Report): Fiscal policy discipline; Redirection of public spending toward education, health and infrastructure investment; Tax reform - Flattening the tax curve: Lowering the tax rates on proportionally high tax brackets (typically above median income), and raising the tax rates on the proportionally low tax brackets (typically below median income); lowering the marginal tax rate; Interest rates that are market determined and positive (but moderate) in real terms; Competitive exchange rates; Trade liberalization - replacement of quantitative restrictions with low and uniform tariffs; Openness to foreign direct investment; Privatization of state enterprises; Deregulation - abolition of regulations that impede entry or restrict competition, except for those justified on safety, environmental and consumer protection grounds, and prudential oversight of financial institutions; Legal security for property rights. See Willimason's "Did the Washington Consensus Fail?" at <http://www.iie.com/publications/papers/paper.cfm?ResearchID=488>; also "Diversity in Development: Reconsidering the Washington Consensus (Jan Joost Teunissen and Age Akkerman (eds.), December 2004, book, pdf)" at <http://www.fondad.org/publications/diversity/contents.htm>; "What is Wrong with the Washington Consensus and What Should We do About it?" by Paul Davidson, Editor, *Journal of Post Keynesian Economics.* Paper presented at Conference on "Reforming the Reforms: What Next For Latin America ? ", Rio De Janeiro, July 25, 2003. See also "The Economics of Empire - Notes on the Washington Consensus" by William Finnegan, *Harper's Magazine* May 2003, available at <http://www.mindfully.org/WTO/2003/Economics-Of-EmpireMay03.htm>

[13] For more discussion on the revolving door and Wal-Martisation trends, see Annexure 4, *Unfairness of Free Trade and* the medley of reactions from American public at <http://www.pbs.org/wgbh/pages/frontline/shows/Wal-Mart/talk/>. See also "On Opinion Page, a Lobby's Hand is Often Unseen", <http://www.nytimes.com/2005/12/23/>.

[14] See also: "Trading Health Care Away? - GATS, Public Services & Privatisation" at

<http://www.southcentre.org/info/southbulletin/bulletin15/southbulletin15-03.htm.>. Some of the sentence formulations of the first four points are taken from the site.

[15] See also "Pharma Pricing in India: a Failure of the Market(s)?" in *Impoverishing the Poor: Pharmaceuticals and Drug Pricing in India.* LOCOST/JSS, Vadodara/Bilaspur, India, 2004.

[16] *Who's got the power? Transforming health systems for women and children*. Millennium Project, MDG Task Force Report, Earthscan, London, 2005, p.17 ff of the Summary Report.

[17] See "Pharma Pricing in India: a Failure of the Market(s)?" op.cit.

[18] Quoted from "Patent Nonsense: Companies Now Demanding Intellectual Property Rights Were Built Up Without Them", by George Monbiot, March 12, 2002 in the *Guardian*, London. Data quoted from Eric Schiff's 1971 study *Industrialization without National Patents.*

[19] Referring to the pharma market, a doctor friend of the writer said: "In no other situation in life does a consumer buy goods of which he/she has no knowledge, buys on the written recommendation of a second party from a third party; and the second party may charge heavily for doing so; and the second party may also get paid by third party and other parties manufacturing those goods; and bought usually at a time of severe distress with death as a possible threat of non-purchase.

[20] See Marcia Angell, 2004, op.cit. Especially Chapter 4, "How Much Does the Pharmaceutical Industry really spend on R &D?"

[21] See <http://www.healthyskepticism.org/ >, site of *Healthy Skepticism*. For countering misleading drug promotion as also for an idea of drug company initiatives, see <http://www.nofreelunch.org/>.

[22] See box below for "Definitions and Key Dates in TRIPS/IPR Related to Medicines" for a glossary of the terms used in this paper related to IP (Intellectual Property) and TRIPS (Trade-Related Aspects of Intellectual Property Rights).

[23] December 17, 2005. "Joint NGO Statement on Need for WTO Moratorium on Regional and Bilateral Trade Agreements and Policies Undermining Access to Health." At <www.cptech.org>.

[24] See also, MSF: *Access to Medicines at Risk Across the Globe: What to Watch Out for in Free Trade Agreements with the United States* at <http://www.accessmed-msf.org/documents/ftabriefingenglish.pdf>

Even as we go the press (Dec 2005) comes the news of Tonga. Tonga has been forced to give up more on tariffs than any of the countries involved in its negotiations to join the WTO, including countries like New Zealand, the USA and the EU, all of whom played active roles in the working party. In fact, its bound tariffs are lower than any other country in the history of the WTO, with the sole exception of Armenia. Tonga will be allowed up to a maximum of 20% tariff on all products. This contrasts with the 350% tariff that the US applies to beef imports, and an equivalent tariff of over 300% that the EU uses to block sugar imports into its market.

[25] Center of Concern/ International Gender and Trade Network. "The Gender Impact of CAFTA" at <www.wola.org/economic/brief_cafta_gender.pdf>

[26] Weissman, R. "Dying for Drugs: How CAFTA Will Undermine Access to Essential Medicines." *Essential Action*, March 2004 quoted in (25).

[27] Moreno, R. The Free Trade Agreement between the United States and Central America: Economic and Social Impacts, p. 118. Quoted in (25).

[28] "Women in Forestry", WRI-http://www.wri.org/biodiv/women-02.html quoted in *Gender Impacts of CAFTA,* The International Gender and Trade Network and Center for Concern, <http://www.igtn.org/>

and <*http://www.cispes.org/english/Campaign_Against_CAFTA_FTAA/cafta_docs/gender_cafta.pdf*>

[29] James Love at "Making enemies - the US/Thai FTA negotiations are bitter medicine" at <http://www.huffingtonpost.com/james-love/>, Jan 11. 2006.

[30] See for instance: *The Truth About the Drug Companies: How they deceive us and what to do about it.* Marcia Angell. Random House, 2004.

[31] Bhagwati, Jagdish. "From Seattle to Hong Kong", op.cit; and see also Annexure 1.

[32] The writer would like to acknowledge Dr Gulhati, Editor, and MIMS India for this terse summary.

[33] Article 8 for instance says among other things:

1. Members may, in formulating or amending their laws and regulations, adopt measures necessary to protect public health and nutrition, and to promote the public interest in sectors of vital importance to their socio-economic and technological development, provided that such measures are consistent with the provisions of this Agreement.

2. Appropriate measures, provided that they are consistent with the provisions of this Agreement, may be needed to prevent the abuse of intellectual property rights by right holders or the resort to practices which unreasonably restrain trade or adversely affect the international transfer of technology.

Article 31 deals with "Other Use Without Authorization of the Right Holder" and 31 (f) says "any such use shall be authorized predominantly for the supply of the domestic market of the Member authorizing such use."

[34] *Who's got the power? Transforming health systems for women and children*. Millenium Project, MDG Task Force Report, Earthscan, London, 2005, page 100.

[35] See for instance: a) *The Biopiracy Factsheets.* Research Foundation for Science Technology and Ecology, Dehradun, 1998. b) *The Basmati Battle and Its Implications For Biopiracy & TRIPs* at <http://www.navdanya.org/articles/basmati_battle.htm> by Vandana Shiva. c) Also Shiva, Vandana. *Biopiracy*. Research Foundation for Science Technology and Ecology , Dehradun, 1997.

[36] See also *Touch-me-touch-me-not, Women, Healing and Plants*, Kali for Women, 1997, New Delhi.

[37] For one suggested model see: <http://www.cptech.org/ip/health/rndtf/> or <http://www.cptech.org/workingdrafts/24feb05WHOen.pdf>

[38] Quoted in: Guitelle Baghdadi, Pharm.D., M.P.H. "Gender and Medicines: An International Public Health Perspective". *Journal of Women's Health,* Jan 2005, Vol. 14, No. 1: 82-86

[39] Quoted in Carlos M. Correa. *Patent Law, TRIPS, and R&D Incentives: A Southern Perspective.* CMH Working Paper Series Paper No. WG2: 12, November 2001.

[40] See Chapter 5, "What they could be? Drug costs in treatment of common and important illnesses and affordability of treatment costs" by -Anurag Bhargava in *Impoverishing the Poor: Pharmaceuticals and Drug Pricing in India.* LOCOST/JSS, Vadodara/Bilaspur, Dec 2004.

[41] Many people are now proposing a better way -- global agreements that focus on R&D rather than high drug prices, and which recognize both innovation and access as important policy goals. See:
<http://www.cptech.org/ip/health/rndtf/bridges042004.pdf>
<http://www.cptech.org/workingdrafts/rndsignonletter.html>
<http://www.cptech.org/ip/health/rndtf/kenya11162005.html>

[42] Aziz Choudry, "War, globalisation and the WTO: Forever new frontiers" at
<http://www.twnside.org.sg/title/twr151n.htm>

[43] Bhagwati, Jagdish: *In Defense of Globalization.* OUP, New Delhi, 2004, pp.182 ff.

[44] Commentary by Chakravarthy .Raghavan, on the World Bank Study of 1991 "Globalization, Growth and Poverty: Building An Inclusive World Economy,' at <http://www.twnside.org.sg/title/poverty2.htm.>Also see a somewhat similar argument in "Trade Policy Reform as Institutional Reform" by Dani Rodrik of Harvard University August 2000. Paper prepared for a Handbook on "Developing Countries and the Next Round of WTO Negotiations," edited by Bernard Hoekman and dedicated to Mike Finger. Available at <http://ksghome.harvard.edu/~drodrik/Reform.PDF>. Also in a similar vein is Rodrik's "The Developing Countries' Hazardous Obsession With Global Integration" revised version published as "Trading in Illusions" in *Foreign Policy*, Mar-Apr 2001.

[45] *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*, January 25, 2005, vol. 102, no. 4.

[46] This point is dealt in much greater detail by Marcia Angel (2004) in her book *The Truth about Drug Companies*, op.cit.

[47] Carlos M. Correa. "Social Costs of New Patent Rules", July 3, 1995. He also quotes a World Bank study: According to a World Bank's economist (Julio Nogues, 1990, 'Social costs and benefits of introducing patent protection to pharmaceutical drugs in developing countries') the minimum welfare loss to a sample of developing countries (Argentina, Brazil, India, Mexico, Korea, and Taiwan) would amount to a minimum of US$3.5 billion and a maximum of US$10.8 billion, while the income gains by foreign patent owners would be between US$2.1 billion and US$14.4 billion.

[48] Source: <http://www.corporateeurope.org/observer8/brittan.html#1>

[49] Quoted at <http://www.projectcensored.org/publications/2005/21.html>

[50] See the Public Citizen report "The Other Drug War: Big Pharma's 625 Washington Lobbyists"

at <http://www.citizen.org/congress/campaign/special_interest/articles.cfm?ID=6537>. Also "Drug Makers Pour Ad Money Into Final Days of Campaign" *Wall Street Journal*, Nov 4, 2002 <http://online.wsj.com/article/0,,SB1036374581794129508,00.html?mod=home_page_one_us>

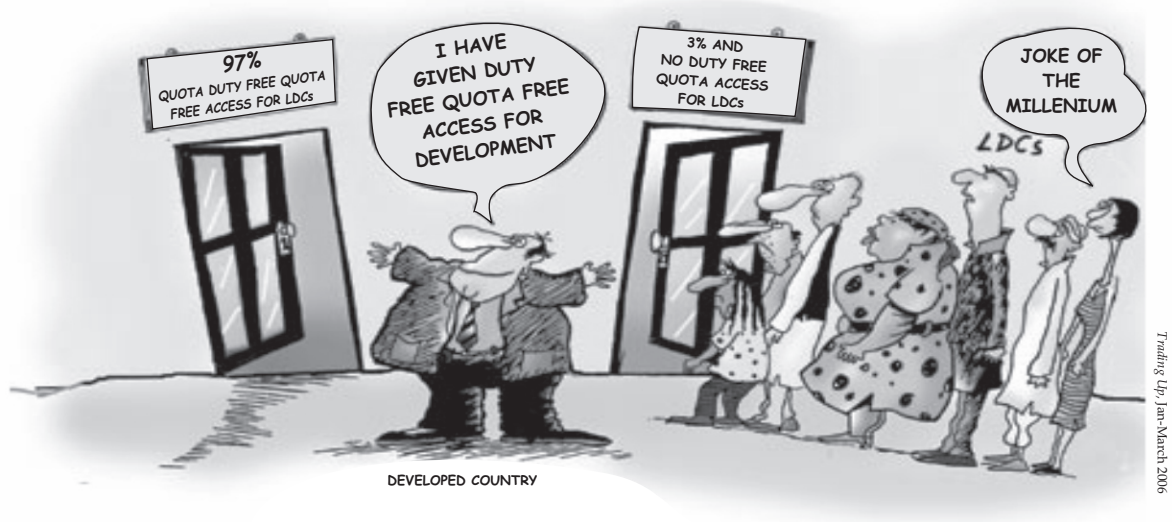
[51] Source: <www.corporatewatch.org/?lid=329#gov>. Other major lobbyists along with Pfizer and other big pharma have been: Pharmaceutical Research and Manufacturers of America (PhRMA), Biotechnology Industry Organization (BIO), United States Council for International Business (USCIB), Business Roundtable (BRT), American Chamber of Commerce (AmCham), American Council on Science and Health (ACSH) and at the global level Structures like the Bilderberg Group, the Trilateral Commission and the World Economic Forum (WEF). Pfizer, as one of the world's biggest multinationals, is heavily involved in lobbying at the global level. The drug giant is a member of major international lobby groups such as the International Chamber of Commerce (ICC) and the World Business Council on Sustainable Development (WBCSD).

[52] Here at the risk of being accused as a conspiracy theorist but the preceding footnotes should suffice.

[53] Interestingly local communities and small towns in USA oppose the establishment of Wall-Mart stores for this reason as well as for spoiling local cultures. See further below. The Center for Responsive Politics reports that Wal-Mart was the sixth largest contributor from the retail industry to the 2000 federal election campaign. Wal-Mart gave over seven hundred thousand dollars, and almost 90% of it went to the Republican Party. The retail industry as a whole favored George W. Bush by a wide margin, giving him $700,000 to Al Gore's $250,000. On the other hand, the industry's favorite candidate in the Senate was Hillary Rodham Clinton, whom it granted $150,000. (see <http://www.theemailactivist.org/Wal-Mart.htm>, <http://Wal-Martwatch.com/>, <http://www.pbs.org/wgbh/pages/frontline/shows/Wal-Mart/talk/>, etc.) Also the review of the PBS film *Store Wars* at <http://www.documentaryfilms.net/Reviews/StoreWars/>

[54] Ravi Kanbur in "Economic Policy, Distribution and Poverty: The Nature of Disagreements"**.**Paper at an invited presentation to the Swedish Parliamentary Commission on Global Development (Globkom) on September 22, 2000. Full revised paper at <http://www.people.cornell.edu/pages/sk145/>

[55] Kanbur, op.cit.


97%
QUOTA DUTY FREE QUOTA FREE ACCESS FOR LDCs
I HAVE GIVEN DUTY FREE QUOTA FREE ACCESS FOR DEVELOPMENT
3% AND NO DUTY FREE QUOTA ACCESS FOR LDCs
JOKE OF THE MILLENIUM
LDCs
DEVELOPED COUNTRY
Trading Up, Jan-March 2006

A Developmental Joke!

Chapter 7
Pricing and Availability of Drugs

People of the same trade seldom meet together even for merriment and diversion, but the conversation ends in a conspiracy against the public or some contrivance to raise prices. - Adam Smith

We have discussed in the earlier chapters on the availability of irrational, hazardous and useless drugs, the poor record of regulatory authorities in India and the drug policies that are at variance with the real health needs of the people of India. In this chapter[1] we discuss a little more on the issue of pricing of drugs in India.

Even though India has a booming drug industry and has contributed to making generics at low prices worldwide, medicines within India are overpriced and unaffordable. The margins are extremely high as we show below. More "players" have not resulted in lower prices of drugs or for that matter lower cost of health services. Demand is supplier induced. The health market creates and promotes wants. Doctors also set themselves as gatekeepers, with societal sanction, to certify various physical states of being including starvation, birth and death.

1. Need for Price Control

The public health system in India is in a state of high disrepair. Privatising public goods and services has only made matters worse. Public hospitals and public health programmes, except in a few states, are underfunded and poorly managed. The budgetary allocation for drug purchase is even less adequately funded, with the result that drugs are regularly "out-of-stock". Poor people are therefore forced to purchase them from the market. Eventually, a significant proportion of them drift to private practitioners on whose rationality there is little control: a vicious circle of poverty, ill health, poor planning and poorer regulation thus sets in.

The process of economic globalisation, which has resulted in further marginalisation of the poor, loss of livelihoods and increasing food, health and economic insecurity, has also further increased the disease burden. The effect on the poor and those who otherwise cannot afford to spend can well be imagined. After dowry, medical care is the second major cause of rural indebtedness in India.[2]

Drug prices have been unaffordable even before the onset of TRIPS from 2005. With the prevalent climate of deregulation and price decontrol, the unaffordability levels of medicines have increased. Drug costs form more than half the treatment costs[3]. India's drug situation in effect is one of poverty amidst adequacy and plenty: people do not have access to affordable health services and medicines even as the share prices of drug companies are booming and Indian drug companies are praised abroad. As we argue below, there is no free market in drugs in India and competition does not work in favour of the consumer most of the time. This makes some form of price regulation of medicines in India necessary. (See box below.)

Why We Need Price Control on Drugs?

- Drugs are overpriced and unaffordable.
- Drugs constitute 50 to 80 percent of health care costs in India.
- Health care is the second-most leading cause of rural indebtedness, after dowry.
- There is no consumer choice of product, price and quality in medicines; only in whether you take the prescribed drug or not, a decision always made in distress, mostly at the threat of death.
- There is no universal health insurance in India; even if there were, regulation of prices would result in considerable savings.

1.1 Drug Pricing Policy Over the Years

Administrative pricing systems for drugs were initiated in 1962, in the wake of the Chinese aggression and the declaration of emergency in 1962. The Defence of India Act was invoked to curb the spiraling prices of medicines. The Drugs (Display of Prices) Order 1962 and the Drugs (Control of Prices) Order 1963 were promulgated. These orders had the effect of freezing prices of drugs as of 1st April 1963. Further attempts to regulate prices were made through the Drugs Prices (Display & Control) Order 1966; the Drugs (Prices Control) Order 1970 promulgated under the Essential Commodities Act 1955 (ECA); the Drug (Prices Control) Order 1979 based on the Drug Policy 1978; the latter policy was an outcome of the landmark Hathi Committee Report of 1975. The thrust of its 224 recommendations was to re-emphasise the leading role for the public sector, the setting up of a National Drug Authority (never set up afterwards), preference to Indian Sector over the foreign sector, indigenous production of raw materials, selective price control on prices of drugs etc. However it is probably the Patents Act 1970 that has had the greatest effect on lowering drug prices and making India's Pharma industry largely a force to reckon with. (See chapter on Patents for further discussion.)

Price controls, after DPCO 1979, have been systematically reduced over the years (see Table 1 "Comparative Chart Summarizing Price Control Scheme under Various Drug Price Control Orders"). Industry did not, and does not, like controls and indeed a major part of the problem was the way price controls were administered. Also since the nineties, there has been a significant paradigm change among policy makers in their view of business and industry. Economic reforms have meant the welcome removal of the licence-quota-permit Raj. There was hope that the attendant corruption would go.[4] With liberalisation, there has been a gradual dilution of the role of the Government even in sectors like health and education, with the naïve hope that the market would take care of the situation.[5] Price control has remained, albeit in a diluted form, and it was the stated aim of the Pharmaceutical Policy of 2002 (henceforth PP 2002) to reduce the "rigors of price control". It was widely expected by industry that about 30 to 34 drugs alone would remain under price control.[6]

Total decontrol, or even a semblance of it, as desired by free marketers, is going to the other extreme and has had, and will have, deleterious effects on not only the poor, but on even the middle class of India. Even the so-called free market countries of the EU and UK have some form of controls price controls, volume controls and cost-effectiveness controls. Twelve out of 16 West European countries control prices of drugs directly (see Annexure 1). On the contrary, it appears, Indian policy makers are intent on throwing out the baby with the drug price control basket.

Table 1: Comparative Chart Summarizing Price Control Scheme under Various Drug Price Control Orders

		DPCO 1979	DPCO 1987	DPCO 1995	Present July 2006
1	No of drugs under Price Control	347	142	76	74
2	No. of categories under which the above drugs were categorized	3	2	1	1
3	MAPE % allowed on normative/ National exfactory costs to meet Post-manufacturing expenses and to provide for margin to the mfrs.				
	Category I	40%	75%	100%	100%
	Category II	55%	100%	N.A.	
	Category III	100 %	N.A.	N.A.	
	(Single ingredient Leader products)				
4	Total Domestic pharma sales covered under Price Control (Approx)	90 %	70 %	50%	–

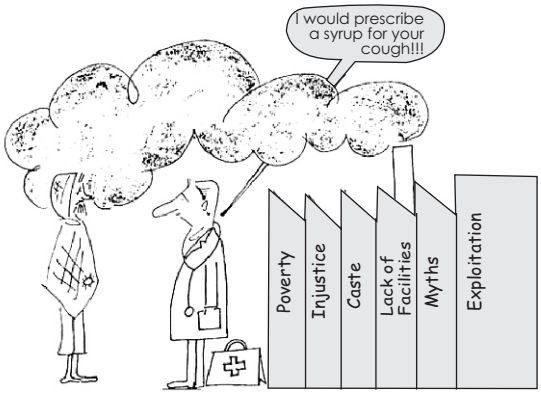
N.A. = Not Applicable

'I became sick because of may poverty,' 'Well, I became poor because of my sickness.'

Global Watch Report 2005-2006

In fact, the *Report of Drug Price Control Review Committee* of the Government of India had noted:[7]

…in most other countries, the regulation of the drug prices is considered necessary to contain public expenditure due to government's role in funding social health and insurance schemes that cover hospital and out-patient drugs. The price regulations are used as an instrument to keep their health budgets within reasonable limits. In these countries, a substantial proportion of the population is covered through health insurance and public health schemes. As a result, the consumers are not affected directly by the high prices of drugs or high costs of medical services, but are made to pay for the increased prices/cost through high insurance premium. As opposed to this, a substantial proportion of the population in India is market dependent and have to meet all their expenses out of their own pocket on this account, making price regulation of pharmaceutical products in the market unavoidable.



Global Watch Report 2005-2006

Nevertheless, in actual behaviour the Government has chosen to ignore this advice as evidenced most recently by its intentions to "lessen the rigors of price control" in the Pharmaceutical Policy 2002. The 2002 Policy itself is riddled with illogic as pointed out in a Supreme Court Petition by AIDAN and others.[9] Briefly, PP 2002[8] and all previous policies (except possibly the first one in 1978) have some common problems: the turnover-based, market share criteria chosen to keep drugs in and out of price control tend to be faulty and lead to anomalies:

- Most essential and useful drugs are kept out of price control.
- Non-essential and harmful drugs like analgin, phenylbutazone, Vitamin E, sulphadimidine, mebhydrolin, diosmine panthonate and panthenols, bacampicilin, etc., are under price control.
- Drugs for HIV/AIDS, cancer, hypertension, coronary artery disease, multidrug resistant tuberculosis, diabetes, iron deficiency anemia, ORS, tetanus, filariasis, vaccines (new) for rabies, hepatitis B, sera for use in tetanus, diphtheria, Rh isoimmunisation, anticonvulsants and antiepileptics, diptheria, snake bite, suspected rabid dog bite/rabies, etc. fall outside price control (see boxes below).
- Price control, since it is based on market share criteria, produces only partial regulation. Chloroquine for malaria would be under price control but not equally important other anti-malarials.[10] True also for leprosy drugs and analgesics.
- Of the 300 top selling brands in the ORG Nielsen list of October 2003, only 36 (that is only 12 percent) were price controlled
- The rest, that is 88 percent, were not.[11]

There is also a tremendous divergence in the goals of the Pharmaceutical Policy 2002 and the National Health Policy 2002.[12] The former seems to address the needs of the drug industry lobby while the latter is more focused on the real health problems of the country. A tragic dichotomy with the people suffering as a result, a case of the left hand (Chemicals and Fertilizer Ministry) of the Government not concerned with the right hand (Ministry of Health and Family Welfare).[13]

We have discussed in other chapters of this book aspects that make the drug market of India "unique": namely, the prevalence of irrational, unscientific and harmful drugs leading to "therapeutic chaos and nihilism" in the Indian market and among medical professionals; the proliferation of brand names and very little prescription by generic names; the easy availability of medicines across the counter; the poor infrastructure for quality control; weak and poorly staffed regulatory administration; poor regulation of the medical profession, of the retail pharmacists, of the pharmacy profession, and poor drug control; lack of serious prosecution of those selling substandard, subtherapeutic and spurious drugs; prescriptions influenced by aggressive promotion of drug companies leading to over/under prescribing;[14] inaccurate diagnosis, lack of up-to-date knowledge, unethical practices like receiving commissions for prescribing certain drugs and sponsorship by drug companies of individual doctor's expenses as well as of medical conferences, etc.

The important thing to understand is that these distortions in reality vastly enhance the price burden and health care costs to the end user.

1.2 Drug Prices and Imperfect Competition

The basic premise of removing price controls has been that competition will lower prices and that a free market exists, or will exist sooner or later, now that we are in a post-liberalisation era. For example the document *Modifications in Drug Policy 1986* had this criteria: "Drugs in which there is sufficient market competition viz. at least 5 bulk drug producers and at least 10 formulators and none having more than the 40% market share in the Retail Trade (as per ORG) may be kept outside the price control." Any such criteria based on turnover results in the anomaly that atleast some life-saving drugs are out of price control and inessentials are left in the price control basket, a fact we have pointed above in the context of the PP 2002. (See box below, on "Drugs in Price Control and those out of it: Theatre of the Absurd".)

The resulting experience of such ineffective policies has been that prices of drugs have been constantly on the rise.[15] Routine policy assumptions that competition and free market work to bring down prices and make drugs abundantly available have mostly proved not true. Unlike in the case of any other consumer goods, when it comes to the purchase of drugs, the consumer is uniquely powerless (since he/she cannot buy drugs without the prescription of the doctor), vulnerable and in distress (with even the threat of life hanging over him/her), and not aware of the scientific aspects of the drug. For a free market to operate, at the least you need well-informed consumers who can exercise free choice. But in the health sector, the buyer/end user, namely the patient, has no choice. Informed choice involving techno-scientific issues is not possible for the lay consumer. A third party, the doctor/prescriber instead, makes the choice for the consumer. The consumer has no easy way of evaluating doctor's prescriptions and advice. We also show below that competition among manufacturers is anything but perfect. Thus both these assumptions of a free market and that of competition reducing prices are therefore contestable.[16] (See box below.)[17]

There is no Other Situation akin to the Purchase of Drugs by a Patient where

- The consumer may have no knowledge about the goods he/she is purchasing,
- Where the goods can be purchased only on the written recommendation of a third party (who may charge you heavily for doing so), no other situation where the goods are purchased in such distress,
- Where the result of non-purchase of the goods may be death or disability.
- Expensive gifts and heavy discounts are offered to those recommending and stocking particular goods and none offered to those who purchase them.
- There is also no other situation in which a particular company making a particular product can have exclusive rights over marketing and manufacture for a period of 20 years.

1.3 Brand Leader as Price Leader

Table 2 gives further justification of our assertion of weak and imperfect competition. If we go through the column on market share it shows that for most of the products, around 40-50 % of the market share is cornered by the leading 3-4 products. This happens in almost all the products. All the drugs mentioned in the table are antibiotics and antibacterials of one kind or the other. All but one, namely cefotaxime, will be out of price control as per PP 2002.

In all these (in Table 2) we find that the top-selling brand of a particular category often is also the higher

priced and most of the times the highest priced. The brand leader is also the price leader. If true competition and free market characteristics were present, the brand selling at the lowest prices would be the brand leader, that is the top-selling brand. The conclusion to be drawn is that competition does not always work in pharmaceuticals, at least in the retail market in bringing down the prices, especially when there are many players, and therefore price regulation is necessary. Competition seems to work in bringing the price of the monopoly producer in the early stages of the product life cycle of a drug formulation. But when the company knows that the sensibilities of the consumer/patient can be played upon, then the same drugs are priced to attract the high-end consumer.

Drugs in Price Control and those out of it: Theatre of the Absurd[18]

If you look at the list of drugs that are *out of* price control, one would be amazed to see the following critical drugs in the list despite selling at variable prices in the market: ORS, very useful in certain types of diarrhoea; all anti-cancer drugs; drugs for TB (like INH, ethambutol, pyrazinamide); drugs for malaria (primaquine, quinine, artemesin); all drugs for HIV/AIDS; drugs for leprosy (dapsone, clofazimine); diethylcarbamazine citrate (for filariasis); atenolol, enalapril, hydrochlorthiazide, amlodipine (all drugs for hypertension); glyceryl nitrate, isosorbide nitrate, beta blockers and calcium blockers (for coronary artery disease); vaccines of every kind including cell culture derived rabies vaccine; antitetanus serum, antidiptheria antitoxin; anti-D immunoglobulin; phenytoin, carbamazepine, valproic acid (anticonvulsants for antiepileptics). On the other hand the DPCO list of 74 drugs in price control include hazardous drugs like analgin, phenylbutazone; an outdated drug like sulphadimidine; and non-essential wonders like Vitamin E, diosmine, pantothonate and panthenols and becampacillin.

Considering the pharmaceutical market, where the products determine life and death, it becomes imperative that a different kind of "marketing" structure dictate, keeping in mind that high costs often means a choice between living and dying. We believe that even though marketing "creativity" in the market should be rewarded, it should not be unreasonable to the extent that the inefficiencies and marketing overheads of the market leader be rubbed off on to the consumer. For that is what we are doing when we legitimise a higher price of a brand: reward a company for its inefficiency and inability to sell at a lower price thereby increasing the costs of health care.

There is complete anarchy in drug pricing in India. Drugs are sold at what the market can take. Drug manufacturers are always lobbying for drug price decontrols even as the drug price control basket has irrelevant drugs in price control and useful, life-saving, essential drugs out of it. Price control is itself not effective as the criteria for control has been market share and not essentiality of drugs of the entire therapeutic class. We discuss some specific anomalies below in the wonderland that is India's drug prices.

1.4 Overpricing of 5000 percent and more

This is clear when you compare tender prices of transparent procurement systems like that of Tamil Nadu and Delhi State Governments.[19] This is clearly brought out in Table 8 later below where we show that India's drug market: prices of drugs in well-run government tender procurement systems are often one to three percent of retail market prices![20] This shows if anything the tremendous overpricing without precedent in any other industry in the world. Also this percentage differential in pricing for the public sector and private retail sector is probably true of no other industry in India. Would the booming computer industry sell in the market a laptop at Rs 100,000 and to the government tender for Rs 2000/- to Rs 3000/-? Would a truck manufacturer sell trucks for Rs 5 lakhs

Table 2: Antibiotic Brand Leaders, Market Share and Price Behavior: A Brief Overview

Drug Product	Market Turnover of Product in Rs crores	Brand Name of Product Leader (s)	Market Share of Product Leader (in %)	Product Leader is Price Leader?	Remarks
Cefotaxime Injection	122.02	Taxim	63%	Yes	
Ceftriaxone Injection	136.01	Monocef	35 %	No	Price Leader is Becef
Cefuroxime Tablets	12.82	Ceftum	38 %	Yes	
Cephalexin Capsules	171.26	Phexin Sporidex	69 %	No No	Price Leader Ceff is 10 % more costly
Amoxycillin Capsules	212.45	Mox Novamox	47 %	Yes Yes	
Amikacin Sulphate Inj	69.12	Mikacin Amicin	68 %	No No	
Chloramphenicol Capsules	41.31	Chlormycetin Enteromycetin Paraxin Kemicetine	86 %	Yes Yes Yes Yes	Chloromycetin is the costliest
Ampicillin + Cloxacillin Caps	109.05	Megapen Ampoxin	78 %	No No	
Ciprofloxacin Capsules	272.35	Cifran Ciplox Ciprobid Alcipro	56 %	Yes Yes Yes Yes Yes	Four brands dominate the market; the product is costly; but still would not be in price control as per PP 2002. Currently in price control.
Doxycycline Capsules	63.35	Microdox Doxy - 1	46 %	Yes Yes	
Roxithromycin Capsules	97.60	Roxid	49 %	Yes	
Erythromycin Tablets	95.41	Althrocin Erythrocin	84 %	No	
Azithromycin	62.71	Azithral	30 %	Yes	
Norfloxacin Tablets	53.09	Norflox	61 %	Yes	
Gentamicin	38.08	Genticyn	33 %	Yes	

(All data as per ORG-AC Nielsen Retail Audit, Oct 2003)

in the market and to the government tender for Rs 20,000 even if he had an order of 100,000 trucks at a time?

Table 3 below gives some sample comparisons of drugs made by LOCOST and retail market drugs that indicate the amount of margins available to the trade.

Table 3: Shocking Margins - A Sample Comparison of Generic Medicine Prices and Retail Prices

No	Name of Drug	Strength	Use	LOCOST, Baroda Price June-Sep 2003	MRP of Standard Company as per *Drug Today* April-June 2003
1.	Albendazole Tabs	400 mg	Against worm infestation	Rs 11.00 per strip of 10 Tabs	Rs 9.00 per Tab (strip of 1 Tab)
2.	Amlodipine Tabs	5 mg	Anti-hypertensive (for high BP)	Rs 2.50 per strip of 10 Tabs	Rs 21.77 per strip of 10 Tabs
3.	Amoxycillin Capsules	500 mg	Antibiotic	Rs 19.75 per strip of 10 Tabs	Rs 68.60 per strip of 10 Caps
4.	Atenolol Tablets	50 mg	Anti-hypertensive (for high BP)	Rs 2.80 per strip of 14 Tabs	Rs 20.00 per strip of 14 Tabs
5.	Enalapril Maleate	5 mg	Anti-hypertensive (for high BP)	Rs 3.00 per strip of 10 Tabs	Rs 22.58 per strip of 10 Tabs
6.	Fluconazole Capsules	150 mg	Antifungal	Rs 35.00 per strip of 10 Caps	Rs 29.50 per cap (Strip of 1 Cap)
7.	Glibenclamide Tablets IP	5 mg	Anti-diabetic	Rs 1.50 per strip of 10 Tabs	Rs 3.73 per strip of 10 Tabs
8.	Metformin Tablets	500 mg	Anti-diabetic	Rs 3.00 per strip of 10 Tabs	Rs 6.45 per Strip of 10 Tabs
9.	Paracetamol Tabs 500 mg	500 mg	Fever-reducing	Rs 2.00 per strip of 10 Tabs	Rs 6.90 per strip of 10 Tabs
10.	Rifampicin Capsules	450 mg	Anti -TB	Rs 32.00 per strip of 10 Caps	Rs 59.12 per strip of 10 Caps.

1.4 Same Drug: Different Prices in the Market

For example, amlodipine shows an 862% difference between the cheapest and the costliest in a drug with at least 40 formulators (see Table 4). The multinational has the drug with the maximum price. Similar examples abound in other drugs.[21]

A study published by Roy and Rewari in the Indian *Journal of Pharmacology*[22] that surveyed the variation in prices of 84 formulations used in the management of cardiovascular diseases in the Indian market concluded that variation in prices ranged from 2.8 % to 3406 %. "In the absence of comparative

information on drug prices and their quality it is difficult for physicians to prescribe the most economical treatment. There is an urgent need to provide adequate information to physicians regarding cost, bioequivalence and quality of drugs."

Table 4: Different Prices of Amlodipine

Drug	Brand name	Company	Price per tab. of 5 mg*
Amlodipine 5 mg.	Amlogard	Pfizer	Rs. 4.81
Amlodipine 5 mg.	Stamlo	Dr. Reddy's	Rs. 2.47
Amlodipine 5 mg.	Amlogen	Alkem	Rs. 1.20
Amlodipine 5 mg.	Amlodac	Alidac	Rs. 0.50

Source of prices: April-June 2002 edition of *CIMS*

1.6 Same Drug, Same Company, Different Price

The same drug company prices the same drug under different brand names at different prices, sometime the drugs are "positioned" in the same state for different market segments. For example cefuroxime tablets are manufactured by GSK under the brand names of Ceftum and Supacef at different prices - Rs 80.91 and 63.01 respectively for 125 mg tablets and Rs 150.34 and 144.94 respectively for 250 mg tablets. Similarly ciprofloxacin 250 mg Tablets are manufactured by Lupin under the brand names of Ciprova and Lucipro 250 at different rates of 41.79 and Rs 31.62 respectively. Again, gentamicin injection by PCI sells as G-Mycin and Gentasporin at Rs 6.80 and 7.68 respectively.

The DPCRC [Drug Price Control Review Committee 1999, Chapter VI, Summary and Recommendations, 11 (vii)] had this to say:

> "It has also been observed that some of the manufacturers tend to provide unduly high trade margins, adversely affecting the consumer interest. Therefore, the committee is of the view that to discourage unethical practices by the players, the difference between the first sale price of a formulation by the manufacturers and the retail price printed on the label be limited to a maximum of 40 percent of the MRP in the case of decontrolled formulations."

Wilful ignorance of government's own committees?

1.7 High Profiteering in Generics Too

If you thought that high profits, indeed profiteering, was limited to brand name drugs, you are likely to be mistaken. High profits are found in the range of 1000 to 2000 percent in the branded generics segment. They are sold to the trade at low prices but the MRP is very high, often exceeding the cost of the equivalent drugs.[23]

> …the profiteering is rampant even in cases of controlled drugs. Take the case of ciprofloxacin, a widely prescribed drug under DPCO. The ceiling price of a strip of 10

tablets of 500 mg is fixed around Rs.60. Against this, a number of leading drug units are selling the ciprofloxacin generic to the stockists at a price ranging Rs.13 to Rs.17. The margin to the retail trade in this case is undoubtedly prohibitive. Such profiteering is highly unethical and also in contravention of DPCO. DPCO clearly says that Maximum Allowable Post Manufacturing Expenses (MAPE) should not exceed 100 percent. In that case, the maximum retail price should be around Rs.26 per strip of ciprofloxacin which should include retail trade margin of 16 percent. Like ciprofloxacin, there are quite a few controlled drugs overpriced by the manufacturers. Drug units are also intensely competing each other by offering higher margins to the trade for pushing up the sales ...[24]

1.8 Export Prices Lower than Local Prices[25]

Indian companies - and sometimes the same Indian companies who violate the drug price control order at home - sell medicines at dramatically lower prices in neighbouring countries. For example the prices of Aceten (Captopril) marketed by Tridoss sells at Rs 3.50 in India and at SL Rs. 0.79 (Indian Rs. 0.35) in Sri Lanka.

In a survey done of Indian drug company product prices in Sri Lanka, in 5 out of 24 medicines the Sri Lankan price was more than the Indian price. In 4 out of 5 medicines the manufacturer was from India. The maximum difference was 25% more than the Indian price and the minimum difference was 10%.

In 19 out of 24 medicines (nearly 80%) the Sri Lankan price was lower than the Indian retail price. The maximum difference between Sri Lankan and Indian prices of most sold drugs was of the Sri Lankan drug being 98% less than the Indian price and the minimum difference was 30% less than the Indian price. In 8 out of 19 instances of lower prices of medicines, the manufacturers were from India. In one instance the same drug (Captopril) manufactured by the same company was 10 times cheaper in Sri Lanka than in India.

However as the box below on "Industry's New 'Innovative' Arguments" points out that drugs are sold at higher, lower and same prices as domestic prices. Indeed the only criteria seems to be both locally and internationally to sell at what the market can take. Which means at the perceived (not the same as real, scientific) value of the drug.

1.9 Stranglehold of Retail Pharmacists: 'A Parallel Government'

Primary bulk drug manufacturers and formulation manufacturers do make a handsome return on their investment. We have seen above the scope of markups. In fact one of the most vested interests in the pharma market who would resist a rational pricing and drug policy tooth and nail are the retail pharmacists and their lobbies. This is because irrational drugs and tonics and syrups often enjoy 500-1000 percent trade margins. Adding to these margins are the free schemes which are seldom billed. Now these margins are available even in generic drugs, which are otherwise rational. The situation in this regard in small towns and taluka level places and in states with relatively weak drug administration is really alarming. Drug producers are at the mercy of retail pharmacists (at last count more than 400,000 all over India).[27] But in this the drug producers are also to be blamed. They bribe doctors as well as retail

Industry's New "Innovative" Arguments[26]

Recently noticing that popular and political wind is blowing for increasing, rather than, reducing the span of drug regulation, the industry has come up with some "innovative" arguments. Let us examine their validity.

Argument No. 1: If drug prices are controlled, there will be no money to fund future research in discovering new medicines.

Response: Do companies expect poor patients of India to pay them artificially-hiked prices of existing medicines (discovered abroad for which the companies have not paid a single paisa) so that in their sole discretion, they may spend money on R&D (a risky affair) ostensibly to discover new medicines and if at all they succeed, then sell them at their self-determined prices? This would mean that their toasts are buttered on both sides! Indian pharma companies are sitting tight over huge reserves. Let them put this money into R&D.

All over the world companies, not in just pharma but in all fields, first put in their own funds into research and then if successful they sell their products at a premium to recoup developmental costs.

If conceptually this line of industry's argument is accepted then why restrict it to pharma sector? Why not allow telephone instrument manufacturers to jack up the prices, so that the excessive profits can be ploughed back into telecom research? The only and correct way to encourage R&D is for the government to give suitable incentives (for example, total excise relief, for say five years, if the company produces a commercially successful novel product), income tax rebates (already available) etc. and provide infrastructure at reasonable cost. To ask poor patients to pay for R&D in advance in the commercial interest of companies is strange and selfish to say the least.

In any case, as of date R&D is merely a convenient argument to keep the profits high. The cost of discovering a new drug up to commercial exploitation in the West is Rs. 3,700 crores and this money has to be spent by one company and not all of them put together. Assuming that Indian cost is just 700 crores (based on purchasing power parity of Indian currency at 5.29 times that of US dollar), no Indian company spends even one-third of this amount on R&D. In fact last year (2003-2004), all Indian companies put together spent 660 crores on R&D, not to mention the fact that many non-R&D expenses are routinely booked under this heading to save on taxes. As of date, R&D is merely a slogan: Not one successful new medicine has come out of India in the last three decades!

Argument No. 2: All price control efforts land in litigation and there is already a big backlog. Besides National Pharmaceutical Pricing Authority (NPPA) has a small staff and the task is too big.

Response*:* Does it mean that people should suffer and pay through their nose because of administrative or legal failure? It is no secret that many defective orders are deliberately issued with large loopholes so that companies can get around the law.

Argument No. 3: Pharma companies cannot export at a price more than what they are selling within the country; therefore there will be national loss.

Response: Of all the arguments given in favour of free-for-all price regimen, this is the most strange and self-serving.

Conceptually, the dynamics of export are entirely different from domestic marketing. There is adequate documentary evidence with the Customs Department to prove that:

Some drugs are being exported at half, if not less, the domestic prices.
Some drugs are being exported at nearly the same rate as domestic prices while
Some medicines are being exported at twice the domestic prices.

Also domestic prices of the same molecule vary a great deal; sometimes, more than 100 per cent (example: Amlodipine). Hence the argument is devoid of any merit. Examples:

Export at lower prices: Fracillin (ampicillin) 250mg exported at Rs. 6.05 (Freight On Board- FOB) while the domestic price is Rs. 22 (exclusive of excise and trade margins).

BQL (enalapril) exported at Rs. 11.37 (FOB) while the domestic price is Rs. 22 (exclusive of excise and trade margins).

Ampicloxacillin 250/250 exported at Rs. 11.48 (FOB) while the domestic price is Rs. 20 (exclusive of excise and trade margins).

Export at equivalent prices: Zentel (albendazole) exported at Rs. 11.53 (FOB) while the domestic price is Rs. 10 (exclusive of excise and trade margins).

Calcigard (nifedipine) exported at Rs. 6.75 (FOB) while the domestic price is Rs. 6 (exclusive of excise and trade margins).

Export at higher prices: Jocet (cetirizine) exported at Rs. 35.77 (FOB) while the domestic price is Rs. 13.94 (exclusive of excise and trade margins).

Besides, there is no monolithic "Indian Pharma Industry" acting in unison. Various companies are in fierce competition with each other and undercutting each other abroad. For example, Herpex (acyclovir) brand was exported to Lusaka at Rs. 36.49 but it was undercut by Vivorax brand at Rs. 20.37. Similarly Stamlo (amlodipine 5mg) was exported to Male at Rs. 2.21 but undercut by Amlodac at half the price Rs. 1.12.

Therefore, domestic retail prices are not and can never be the basis or yard stick for export policies and prices. They are based on actual costing and opportunities available abroad. Besides, more than half of exporters do not have domestic retail sales (such as Divi's, Matrix etc.) and hence they are not concerned with domestic prices. Similarly, every Indian company retailing at home is not involved in exports. Assuming that the argument was conceptually valid, why should non-exporters get undue benefit at the cost of poor patients?

As per Pharmexcil data, total pharma exports in 2003-2004 were around Rs. 14,000 crores. Out of which about 60 per cent (approximately 8,500 crores) are bulk drugs and intermediaries. Consumers in India are not affected adversely by export pricing of bulk drugs. The export of finished medicines (ready-to-consume) is about Rs. 5,500 crores out of which regulated markets (Western advanced countries) account for about 30 per cent (Rs. 1600 crores) and balance (Rs. 4,000 crores) goes to unregulated markets in developing countries.

Domestic formulation prices have nothing to do with exports to advanced Western regulated markets because extensive and stringent rules of quality and manufacturing facilities apply requiring pre-approval inspections severely limiting the number of competing exporters. No one in USA expects to get 10 tablets of Ranitidine 150mg for Rs. 4 (US 10 cents) when the domestic price in USA is US$ 5.

Domestic marketing is 'doctor-and-chemist centric' since consumers (patients) do not decide which, in what quantity and when to buy medicines. The entire thrust is to 'convince' prescribers and retailers. On the other hand exports are 'buyer-centric.' : an importer or actual user in Vietnam will only buy medicines from Indian exporters if the price suits him. He will shop around the world to find the lowest price. The importer in Vietnam will not look at Indian domestic prices. If the buyer, irrespective of domestic prices in India, finds a cheaper source he is not going to oblige companies in India.

Even otherwise domestic prices cannot be pegged simply to help exports. If this concept is accepted then all prices, such as tea, bicycles, iron should be hiked so that exporters in India can sell their merchandise abroad! Asking poor patients of India to pay higher prices for medicines so that companies make excessive profits twice local sales and export earnings is a unique, never-heard of argument in the past.

Argument No. 4: Why control only medicine prices when everything else in health care services is not controlled?

Reply: It is a skewed argument. The solution is to regulate all healthcare costs by increasing (like England) the resources for state medical care rather than throwing poor people at the mercy of private profit-making institutions. It is shameful that on the one hand, Planning Commission admits that over 35% of people in India live below poverty line and on the other hand 80% of all people depend on the extremely expensive, unaffordable private sector for their health needs.

Argument No. 5: Drugs are only a small part of health care expenses. So why are you focusing on this?

Response: Drugs are not that small a part as it is made out to be. They constitute over 40% of cost of treatment, the single largest component. The sum of 18,000 crores of medicines being sold by the organised sector in the domestic

pharmacists to push sales. Retail pharmacists refuse to sell products of particular companies if margins are not increased.

> To increase their leverage over drug companies, pharmacy owners banded together into trade associations. The associations launched boycotts against drug companies to win higher profit margins. The associations also began demanding that drug companies obtain a "no-objection letter" from each state trade association before a new drug could be sold there. Otherwise it would be excluded from the pharmacists' stock lists. For each new drug, the trade groups usually solicit a cash donation….
>
> Dilip Mehta, president of the All India Organization of Chemists and Druggists, which represents 500,000 Indian pharmacists, boasts of how his association also has forced drug companies to sign "memorandums of understanding" in which they agree to increase profit margins to pharmacies.
>
> "They have to surrender," Mr. Mehta says, speaking from his tiny office at the rear of a wholesale apparel center in Bombay. The chemists association, he says, is like "a parallel government."[28]

1.10 Comparison with Earnings of a Wage Labourer

What is the implication of this profiteering for a laborer, who earns Rs. 60/- a day? Anurag Bhargava has worked this out in case of ten common illnesses (see Table 5). In the accompanying table, the cost of drug treatment is compared for some common illnesses in terms of number of days of earnings that a laborer would have to spend to buy these drugs. This table gives an idea about how hard it is for a laborer to buy these exorbitantly costly drugs in his struggle for survival. (For more details see *Impoverishing the Poor,* LOCOST/JSS, 2004.)

Table 5: Drug Costs and Person Days in Terms of Wage Labour

Problem	Upper level of drug costs	No. of person-days to be spent in earning the drug cost
1. Streptococcal pharyngitis (sore throat)	Rs. 109.8	1.80
2. Bacillary dysentery	Rs. 84.2	1.40
3. Treatment of iron deficiency anemia for 6 months	Rs. 3744	62.40
4. Tuberculosis treatment for 6 months	Rs. 2616	43.60
5. Treatment of multi-drug resistant TB for 18 months	Rs. 44190	736.00
6. Hypertension treatment for 1 year	Rs. 1076.75	17.95
7. Diabetes mellitus with oral drugs like glicazide	Rs. 2073.2	34.50
8. Coronary artery disease	Rs. 12541.4	209.00
9. Prevention of Hepatitis A	Rs. 1856	30.90

2. Health and Political Context of Price Control

These trends have to be viewed in conjunction with the burgeoning crisis in non-communicable diseases in India (see box below). We also briefly discuss in the accompanying box why drugs for non-communicable diseases have to be placed under price control.

2.1 Crisis of Non-Communicable Diseases

The crisis in health status has deepened with *widespread occurrence* of the HIV epidemic, *increasing prevalence* of hypertension, diabetes mellitus, ischemic heart disease, cancer and *increasing drug resistance* in infections such as tuberculosis, malaria, typhoid, and other bacterial infections.[29] Moreover, post-2005, the possibility of India's pharmaceutical industry reverse engineering newer drugs, has diminished unless the Government issues a Compulsory License and new drugs patented by foreign companies are subject to price control. This is easier said than done because it needs an exercise of political and moral will, against the financial clout of the big pharma.

The Doha Agreement has clarified TRIPS flexibilities, including the primacy of a country's public health needs. Unfortunately this interpretation has not been used either in the provisions of the recent April 2005 Amendments of India's Patents Act regarding more liberal grounds for compulsory license ("…each member has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted…") or for defining what drugs can and cannot be patented. Clearly the amendments to the1970 Act could have said that drugs of a certain therapeutic class important for certain crucial disease situations prevalent in India are outside the purview of the patent regime. There is also no statement in the amendments whether newly patented drugs will be subject to price control.

Pharma industry has to match its production to disease priorities and patterns prevalent, unlike in India at present; and the kind of drugs made needs to be regulated.

Crisis of Non-Communicable Diseases in India

A major public health crisis, which has arisen in the last few decades with the demographic transition, increasing urbanisation, and lifestyle related factors, is the increasing prevalence of a host of non-communicable diseases. Some problems related to iron deficiency anemia, low nutrition and poor sanitation, have remained.

Consider the following:

Anemia: Anemia is a major public health problem in women and children with a prevalence of 74.3% in children of 6-35 months and a prevalence of 49-56% in women (NFHS 1998/99). Anemia contributes to 1/3 of maternal mortality.

Diabetes: India has the highest number of patients with diabetes in the world with estimates ranging from 19.4 million in 1995 to around 32.7 million affected. An increasing prevalence of diabetes in urban areas has been documented.

Hypertension: The number of patients with hypertension is also high with an estimated prevalence in adults of 20-40% in urban areas and 12-17% in rural areas.

Coronary artery disease: The prevalence of coronary artery disease in urban areas is estimated to be 10% in people over 35 years of age.

Chronic respiratory diseases: These include bronchial asthma, and chronic obstructive airways disease. Morbidity from respiratory diseases accounts for 65 million cases and 580,000 deaths.

Cancer: Estimates of age standardised rates of cancer range from 99.0 to 129.6 per 100,000 in males and 104.4 to 154.3 per 100,000 in females. About **700,000** new cases with cancer occur each year.

Source: The burden of non-communicable diseases in South Asia. *British Medical Journal*, April 2004.

Why should Drugs for Non-Communicable Diseases be Placed under Price Control?

The degree of morbidity and mortality associated with these non-communicable diseases mean that patients with hypertension and diabetes mellitus would be more than the entire populations of many developed countries..

These diseases often carry the burden of lifelong therapy

Drugs for diabetes, hypertension, asthma, have to be taken life-long, for epilepsy for a minimum of 3 years. Costs of treatment impose a tremendous economic burden on patients, which many cannot afford and suffer premature death or other complications like stroke, heart failure and kidney failure.

Patients with non-communicable diseases most often have to take multiple medications, which further adds to cost.

For instance, patients with diabetes may have to take two different anti-diabetic pills, in addition to drugs for hypertension (which often coexists), for cholesterol reduction, etc.

The average cost of care for a patient with diabetes is estimated to be Rs 4500 per year;[30] a lower socio-economic group person may have to spend 59 percent of his income on this.[31]

We calculate that the cost of the multiple medications for coronary artery disease according to the market leader rates is Rs. 12,500 per year, clearly unaffordable. This figure can be brought down to less than 20 percent if more rational pricing regimes were in place.

Most of these drugs are at present outside price control, and there is evidence of wide inexplicable differences between brands made by reputed companies that vary by 400-900 percent in their retail prices, which indicates profiteering by the companies at the cost of the patient.

2.2 Role of Governments in Medicine Price Regulation

The pharma market is riddled with asymmetries between patient-doctor, doctor-drug company and patient--drug company. The patient as end-user does not have a choice in decision making: whether to buy a drug or not. The doctor makes the decision for him/her. It is for these reasons, the State cannot play merely the " neutral" role of an arbiter but needs to proactively intervene in favour of the consumer. It is for these reasons, even in advanced market economies, governments actively intervene to provide affordable and accessible health care services. Price regulation of medicines, therefore, is the norm all over the world, except the USA, which unfortunately India is trying to emulate.

Even in USA, drug companies and health insurance companies always negotiate prices. But the system excludes large numbers of the poor and especially makes medicines costly for the elderly. [32] One in three non-elderly Americans -- 74.7 million -- was without health coverage for all or part of 2001-2002.[33]

UK has its Pharmaceutical Price Regulation Scheme.[34] All European Union (EU) countries have a form of price regulation. In setting prices, these countries use therapeutic comparators and the price of products in other EU markets. Denmark, Greece, Finland, Ireland, Italy, the Netherlands, Portugal, and Sweden set a maximum price in relation to prices in neighboring countries. Belgium, France, and Italy set prices in relation to relative cost, prices elsewhere in the EU, and the contribution made to the national economy. In Austria,

France, and Spain there are volume-cost and other rebate schemes. Spain and the United Kingdom set their prices to ensure a rate of return within a particular profit range.[35]

Canada has a Patented Medicines Prices Review Board, France has a Transparency Commission and Economic Committee on Medicines, Egypt has all drugs under price control, Italy has restricted wholesale margins, Germany has its reference pricing system. Some system of price monitoring and price regulation prevails in Japan, Netherlands, China, Indonesia, Colombia, etc. In some of these countries, drug pricing is tied with national health system reimbursements and or insurance schemes. Big pharma lobbies like PhRMA in response say: "Foreign price and access controls on pharmaceuticals distort and inhibit International Trade" and want the US Government to "take action", meaning twist arms in other ways.[36] Indeed, it is worth pondering, how come all the developed free market economies do not have a free market with respect to pricing of medicines?

In the absence of universal free access to health insurance and/or meaningful price controls, in India, the havoc on the majority of the population can well be imagined.

2.3 What about R & D?

One of the reasons given for high price of drugs is the high R&D and innovation costs in pharma. But this is wrong (see also Argument No 1 in the box above on *Industry's New 'Innovative' Arguments*). Does any other sector say that they have to price a product high because they are doing/have done R&D for future/present products? Do manufacturers of computers or microprocessors or cars do so?

Secondly the cost of doing clinical trials is about $300 million per drug (See box below on *Executive Summary of Public Citizen Congress Watch Report*.). About 80 percent (Rs 1000 crores) of this has to be done in the west if it has to be accepted there. This is apart from the Western pharma industry's figures where the cost of discovering a new molecule is stated as $ 800 million per drug, which includes $ 400 million as opportunity costs of not doing R&D! Using purchase-parity, this is Rs 700 crores *for a single drug*. It is not possible at present sales and projected sales of Indian companies for Indian drug companies to spend such amounts on R & D. Indian companies together spent Rs 660 crores on R& D in 2003-04. No drug has been discovered, tested and marketed by Indian companies in last 20 years, despite promise of exemption from price control for 15 years. (See also below the chart *How much does it Really Cost to Manufacture a Drug* and Chapter 5 for the kinds of moneys spent by the Pharma lobby in America to manufacture consent – of course true for India too.)

Prices of drugs seldom increase in the West. If R&D costs are recovered in the first year or so (first few weeks in many cases), only legitimate profits need recovery thereafter. Following some such logic, in Japan it is mandatory that all prices of all new drugs come down by five percent every year! In our case royalty percent needs to be fixed which has not been done in the 2005 Patents Amendments (usually, not more than five percent).

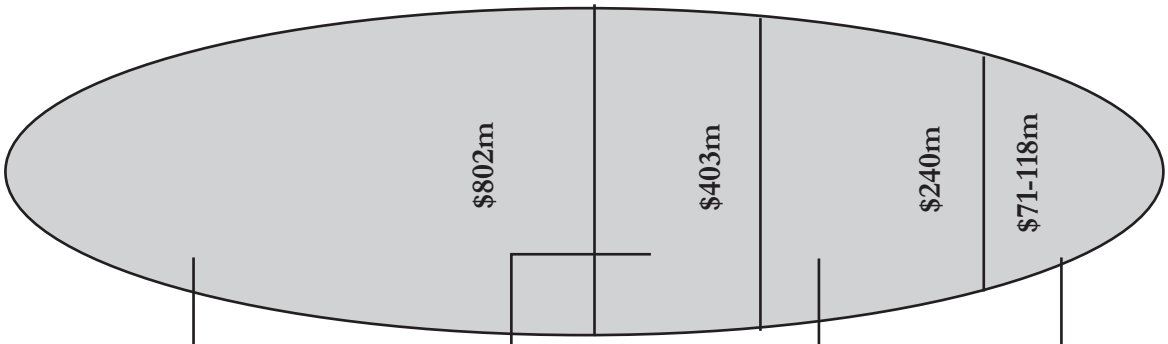
Executive Summary of Public Citizen Congress Watch Report[37]

- The drug industry's claims that R&D costs total US$ 500 million for each new drug (including failures) is highly misleading. Extrapolated from an often misunderstood 1991 study by economist Joseph DiMasi,[38] the US$ 500 million figure includes significant expenses that are tax deductible and unrealistic scenarios of risks.
- The actual after tax cash outlay or what drug companies really spend on R&D for each new drug (including failures) according to DiMasi study is approximately US$ 110 million (based on data provided by drug companies, in the year 2000).
- A simpler measure also derived from data provided by the industry suggests that after tax, R & D costs in the 1960's raged from US$ 57 to 71 million for an average new drug brought to market, including failures.
- Industry R&D risks and cost are often significantly reduced by taxpayer-funded research, which has helped launch the most medically important drugs in recent years and many of the best-selling drugs, including all of the top five sellers in one recent year surveyed (1995).
- Internal documents of National Institutes of Health (NIH), obtained through the Freedom of Information Act, show how crucial the taxpayer-funded research is for top-selling drugs. According to the NIH, taxpayer-funded scientists conducted 55% of the research projects that led to the discovery and development of the top five selling drugs in 1995.
- The industry fought, and won, a nine-year legal battle to keep US congressional investigators of the General Accounting Office from seeing the Industry's complete R&D records. Congress can subpoena the records but has failed to do so. That might owe to the fact that in 1999-2000 the drug industry spent US$ 262 million on federal lobbying, campaign contributions and advertisements for candidates thinly disguised as "issue" advertisements.
- The drug industry's R&D does not appear to be as risky as the companies claim. Each year since 1982, the drug industry has been the most profitable in the US, according to *Fortune magazine's* ranking. During this time, the industry's returns on revenue (profit as a percent of sales) have averaged about three times the average for all other industries represented in the *Fortune 500*. It defies logic that R&D investments are highly risky if the industry is consistently so profitable and returns on investments are so high.
- The drug industry's R&D is rendered less risky by the fact that only about 22% of the new drugs brought to market in the last two decades were innovative drugs that represented important therapeutic gains over existing drugs. Most were "me-too" drugs, which often replicate existing successful drugs.
- In addition to receiving research subsidies, the drug industry is lightly taxed, thanks to tax credits. The drug industry's effective tax rate is about 40% less than the average for all other industries.
- Drug companies also receive huge financial incentives for testing the effects of drugs on children. This incentive called pediatric exclusivity, which the US Congress may reauthorize this year, amounts to US$ 600 million in additional profits per year for the drug industry and that's just to get companies to test the safety of several hundred drugs for children. It is estimated that the cost of such tests is less than US$ 100 million a year.
- The drug industry's top priority increasingly is advertising and marketing, more than R&D. Increases in drug industry advertising budgets have averaged almost 40% a year since the government relaxed rules on direct-to-customer advertising in 1997. Moreover, the *Fortune 500* drug companies dedicated 30% of their revenues to marketing and administration in the year 2000, and just 12% to R&D.

(Reproduced with thanks from: Roy Chaudhury, Ranjit and Nirmal Kumar Gurbani. *Enhancing Access to Quality Medicines for the Underserved.* Anamaya Publishers, New Delhi, 2004.)

How Much Does it Really Cost to Manufacture a Drug?

In November 2001, the Tufts Centre for the Study of Drug Development, which is 65% funded by the industry, came out with a figure of $802m. Public Citizen, a consumer organisation, did a detailed analysis of the figure and concluded that it was inflated by about 75%. In addition, none of the 68 drugs Tufts considered had been developed with the help of government money, unlike the case with many other medicines.



$802m Roughly half of this figure is made up of "opportunity costs" of capital. what the money could have earned if the money had been spent elsewhere instead of on research.

$403m The Tufts study says this is the actual out-pocket R&D cost. But that is before tax. Companies in the US deduct 34% of their R&D expenses under federal tax law

$240m This is the real cash outlay after tax breaks but only for the most expensive drugs, developed without government assistance.

$71-118m This is the figure Public Citizen calculated as the rough R&D cost for new drugs brought to the market between 1994 and 2000 based on data from the drug industry.

Source: *Guardian* 2003, quoted in *Global Health Watch 2005-2006*. <www.ghwatch.org>.

So is pharma R&D risky? No, it does not appear to be any more than any other technology based industry.[39]

> ... Despite all the rhetoric to the contrary, this is not a high-risk industry. As one indication, the law provides tax credits equal to 50 percent of the cost of testing orphan drugs and extends the credits to other drugs if "there is no reasonable expectation that the cost of developing and making available in the United States a drug will be recovered from sales in the United States." In other words, if you can't make a profit, the government will help you out.
>
> Risky businesses have variable returns, but the pharmaceutical industry has been, year after year, the

most profitable in the United States. What these companies are, in fact, claiming is an entitlement not only to recoup anything they wish to spend on R&D but to make an exorbitant profit margin as well.

R&D costs, no matter what they are, have little to do with drug pricing. Mr. Gilmartin, President and CEO of Merck, referring to the $802 million per drug estimate, remarked, "The price of medicines is not determined by their research costs. Instead, it is determined by their value in preventing and treating disease … it is the doctor, the patient, and those paying for our medicines that will determine its true value."

More relevantly, most R&D even in the West is public funded,[40] even when the pharma companies reap the profits. For example, Taxol (anti-cancer drug) was supported by the National Insitutes of Health (NIH). (See box below *Benefits of Drugs with NIH Involvement.*) Drugs like Gleevec, Epoeitin, Zidovudine (AZT) were discovered in public funded university departments. And during 1998-2002, of 415 US FDA applications, only 14 percent were innovations, the rest were me-too drugs. And as far as R&D relevant to tropical countries, only 13 out of 1223 new chemical entities discovered between 1975-1997 related to tropical diseases. Therefore we need different strategies for supporting R&D for diseases of national importance as well as diseases affecting the poor in all countries.

Benefits of Drugs with NIH Involvement

A study of the 21 drugs introduced between 1965 and 1992 that were considered by experts to have had the highest therapeutic impact on society found that public funding of research was instrumental in the development of 15 of the 21 drugs (71 percent). Three-captopril (Capoten), fluoxetine (Prozac), and acyclovir (Zovirax)-had more than $1 billion in sales in 1994 and 1995. In addition to these drugs, other members of the group of 21 drugs, including AZT, acyclovir, fluconazole (Diflucan), foscarnet (Foscavir), and ketoconazole (Nizoral), had NIH funding and research to help in clinical trials.[41] (See table below.)

Generic name *(trade name)*	**Illness**	**NIH role**	**Non-monetary benefits**	**Dollar savings**
Acyclovir *(Zovirax)*	Herpes simplex virus (HSV)	NIH-funded researchers discovered how HSV enters nerve cells and purified HSV enzymes	Prevents neonatal herpes	Reduces treatment in pregnant women with HSV from $1.3 mn. per neonatal infection prevented to $493,000
AZT *(Retrovir)*	HIV	National Cancer Institute helped screen AZT, the first anti-HIV therapy	Reduces transmission of HIV from mother to child in 66% of potential cases	HIV transmission rate from mother to child was 15-30% before 1994; now it is 5-10%
Captopril *(Capoten)*	Hypertension, diabetes-induced kidney failure	NIH funded research to find the drug that would inhibit the enzyme causing hypertension	Reduces risk of kidney failure, dialysis, transplantation, and death in 50% of patients with insulin-dependent diabetes mellitus	Use in patients with insulin-dependent diabetes mellitus saves $32,550 per patient in direct costs and $45,730 in indirect costs over a lifetime
Cisplatin *(Platinol)*	Testicular, ovarian, and cervical cancer	National Cancer Institute developed cisplatin combination chemotherapy for testicular cancer	77% patient response rate for testicular cancer; 60-65% cure rate	Cost savings from testicular cancer treatment average over $156 million a year
Erythopoietin *(Epogen)*	Anemia	National Institute of Diabetes and Digestive and Kidney Diseases funded research identifying the cells that produce the erythropoietin hormone	Reduces need for blood transfusions in anemic patients and allows them to be more vigorous; also reduces mortality	Reduces hospital days for anemic patients from 16.3 days a year to 11.6 days; saves thousands of units of blood transfusions
Fluxetine *(Prozac)*	Depression	National Heart, Lung, and Blood Institute and National Institute of Mental Health researchers discovered serotonin	Avoids side effects prevalent in earlier antidepressants	Lower total cost of health care compared to earlier antidepressants
Tamoxifen *(Nolvadex)*	Breast cancer	National Cancer Institute performed laboratory and live subject testing of the effects of tamoxifen	Five years of tamoxifen treatment reduces breast cancer mortality 26% and reoccurrence 47%; tamoxifen prevents breast cancer in 50% of high-risk patients	Successful tamoxifen therapy saves "end-stage" treatment cost of $22,142 per patient; direct cost savings from tamoxifen use are $41,372 per year of life gained for women 35-49

2.4 Patents, Prices and Medicines

We discussed the issue of patents earlier in Chapter 6 separately. From January 1, 2005, the regime of product patents is in force in India keeping with the so-called obligations under WTO/TRIPS. The questions often asked are: will patents enhance/decrease the availability of drugs? Will it increase drug prices?

The answer seems to be yes. Prices of all new drugs that have patent validity would increase. For some of these reasons:

- Product patents would result in monopoly pricing. The amended Patents Act says, though not in so many words, importation would be treated equal to working of the patent. As long as the drug is not manufactured in India (in which case the Government can actually examine the manufacturing premises and decide on the price to some degree), the Government would have to go by what the monopoly producer says the landed price of the imported drug is.
- Price control of imported drugs and drugs under patent would need a lot of honest political will. So would compulsory license.
- Compulsory license can be issued only after 3 years after grant of the patent. It also has made the issue of compulsory license cumbersome except in the case of national emergency. The Dec 2005 Hong Kong decision has made it even more cumbersome.[42]
- Drugs needed for most frequently occurring diseases would be or are already out of patent. For these drugs, prices would be subject to the usual market vagaries and distortions prevalent in India. We have discussed these in this chapter.

It is all the more necessary that an essential drugs programme be implemented in the country with marketing approval for only rational drugs. Importance of rational therapy and prescription of both patented and generic products, as well as rational, ethical marketing, can reduce the adverse cost impacts. The need for price control of drugs by the government becomes even more significant.

3. Some Positive Initiatives and Reports

The Municipal Corporation of Greater Mumbai (MCGM) is probably the richest such city level corporation in India and the city of Mumbai is the pharmaceutical and business capital of India. But in the health services for the ordinary citizens of Mumbai, there is a great deal of scope for improvement. A drug monitoring exercise at a secondary hospital of the MCGM revealed "that a little more than half (34 out of 60) the drugs prescribed for patients /clients seeking services at gynaecology out-patient clinic were not available on MCGM schedule. These included antibiotics such as norfloxacin and tetracycline, vaginal pessaries (used in treatment of reproductive tract infections), antispasmodics, anti-inflammatory drugs, hormone-based drugs, neuro-regulators and drugs used for treatment of infertility. Most common reason for non-availability of drug was 'Not on MCGM schedule'."[43] (See also Tables 6 and 7 below.)

A review of the drugs listed in the EDL and comparison with the Drugs Schedules of MCGM for May 2001 "showed that, of the 264 drugs listed in the EDL, 140 (53%) were not available on the MCGM drug schedules. Of the 123 drugs categorised in EDL as belonging to 'U' (universal) category, 50 (40.7%) were not on MCGM Schedule."[44]

If this could be the picture in a city like Mumbai, the situation in rural areas can well be imagined. In the well

known study of Satara district of Maharashtra (for a summary of the study, see box "A Study of Drug Shortages in Satara District" in Chapter 2), the drug-supply to the public sector in Satara District was a mere Rs. 5.6 million, as compared to the most minimum, reliable estimate of a drug sale of Rs. 212.8 million in the private sector during 1991-92. The drug supply especially to PHC and RHs (rural hospitals) suffers from chronic gross shortages and haphazardousness. "If the financial resources that were currently spent on unnecessary drugs and irrational combinations are rectified and instead spent on rational drug treatment, there would be adequate resources to take care of all OPD and indoor cases as well as for preventive care in Satara district."

Table 6: Drug Monitoring Exercise at the Secondary Hospital

	n = 148 (%)
All prescribed medicines available at the hospital pharmacy	29 (20 %)
Some medicines or part quantity available at the hospital	32 (22 %)
None of the prescribed medicines available at the hospital	74 (50 %)
Information not available	13 (9 %)

Table 7: Reasons for Non-Availability of Drugs at Secondary Hospital

Reason for non availability of drugs	n= 158*
Not on MCGM schedule	128 (81 %)
Funds not available	13 (8 %)
Not supplied by manufacturer	10 (6 %)
For MCGM employees only	3 (2 %)
For inpatients only	2 (1 %)
Bottle not available	1 (1 %)

Note: * Actual number of medicines that were prescribed but were not available at the hospital pharmacy

3.1 Tamil Nadu and Delhi State Procurement Systems

As against this depressing scenario, there are some positive initiatives both in the public sector and the non-profit service sector.

Most impressive of these are the pooled procurement efforts of the governments of Tamil Nadu, Delhi State (see Chapter 2, section on "Implementation on Essential Drugs Idea in Two States of India") and Orissa. In addition they have effected considerable savings in terms of expenditures on drugs, increased availability of drugs at all levels of government health services, and in general advocated rational use of medicines by formulating standard treatment guidelines. The Tamil Nadu process is also very transparent and the prices of finalized tender awards are on the web (see for instance at <http://www.tnmsc.com/l1rate0304.doc >). See Tables 8-9 below.

A few other state governments namely that of Rajasthan, Maharashtra, Haryana, Himachal Pradesh, Andhra Pradesh, Madhya Pradesh, Karnataka, Assam and Chhatisgarh have also taken steps to regularize their drug purchase list by making the focus on essential drugs and rational medicines and formulating standard treatment guidelines.

Table 8: A Comparison of Tender Rates and Retail Market Rates						
Drug Name (1)	**Name of Tendering Firm (2)**	**Tender Rate (Rs) (3)**	**Unit (4)**	**Mfr of Retail Market Product . (5)**	**Over-price Index Col (6)/(3) (7)**	**Tender Rate as percent of Retail Price (8)**
Albendazole Tab IP 400 mg	Cadila Pharmaceuticals P Ltd	22.60	10×10 tablets	Torrent	52.65	1.89
Bisacodyl Tab IP 5 mg	Lark Laboratories (I) Ltd	16.50	10×10 tablets	German Remedies	43.45	2.30
Alprazolam Tab IP 0.5 mg	Bal Pharma Ltd	3.50	10×10 tablets	Sun Pharma	40.43	2.47
Diazepam Tab IP 5 mg	Pharmafabricon/LOC OST	3.05	10×10 tablets	Ranbaxy	30.33	6.26
Folic acid and Ferrous Tab NFI	Aurochem India P Ltd.	5.89	10×10 tablets	Smith Kline	25.21	3.97
Amylodipine Tab 2.5 mg	Lark Laboratories (I) Ltd	9.10	10×10 tablets	Lyka	16.32	6.13

Excerpted from: Srinivasan, S. "How Many Aspirins to the Rupee? Runaway Drug Prices",*Economic and Political Weekly*, February 27-March 5, 1999.

Table 9: Policy Initiatives by the Delhi Government		
Steps/Vision envisaged in 1994	**Action Initiated**	**Year of Achievement**
Selection of Essential Drugs List	1994	1994
Centralised pooled procurement system	1994	1995
Setting up a system of quality assurance, GMPs	1994	1995
Preparation of the State Drugs Formulary	1994	1997
Training in Rational Use of Drugs (RUD)	1994	1994
Drug information	1995	1999
Preparation of Standard Treatment Guidelines	1995	1998
Establishing ethical criteria for drug advertising and promotion	1995	1996
Conducting research and monitoring in drug use	1994	1995

Source: Gurbani, p.30. in Gurbani N K. "Progress in Rational Use of Drugs in India" in *The Medicines Scenario in India: Perceptions and Perspectives* edited by Banerji A, for Delhi Society for Promotion of Rational Use of Drugs, New Delhi. (undated).

Similarly though not as dramatically, prices decreased and stock position of items increased in Orissa after the Drug Inventory Management System (DIMS).

Among voluntary service sector initiatives, for the last 20 years the Vadodara-based NGO, Low Cost Standard Therapeutics (LOCOST), has been manufacturing a variety of essential drug formulations and selling them directly to its clientele, namely, social action groups and NGOs working for the poor all over India and without the intervention of middlemen. A similar effort of church-based groups called the Comprehensive Medical Services India (CMSI) has been existence in Chennai for the last 10 years. Centralized bulk purchase efforts like that of the CDMU (Central Drug Medicinal Unit), Kolkata, at negotiated prices from a variety of manufacturers, has also seen considerable savings to the institutional consumer. The earliest example, from 1919, is of course the Methodist Church initiative, the All-India Mission Tablet Industry (AIMTI), at Bangarpet near Bangalore.

3.2 Task Force Report

The Government of India appointed a Task Force chaired by Pronab Sen, Principal Adviser at the Planning Commission, "to Explore Options other than Price Control for Achieving the Objective of Making Available Life-saving Drugs at Reasonable Prices". The Task Force submitted its report in September 2005 and if *implemented* they should alleviate many of the gross distortions in drug pricing.[45]

The Task Force Report departs from previous government reports in asserting that "price regulation should be on the basis of 'Essentiality' of the drug and on strategic considerations regarding the impact of price control on the therapeutic class" instead of being based on market shares and turnover which has led to gross absurdities. The crux of the Report's recommendations is on price control. Recognising the corporate allergy to "control", it recommends that as a strategic approach, price *regulation*

> should be applied only to formulations and not to upstream products, such as bulk drugs. No effort should be made to impose a uniform price, and only a ceiling price should be indicated. The ceiling price of essential drugs should normally not be based on cost of production but on readily monitorable market based benchmarks. Other drugs falling into selected therapeutic categories should be brought under a comprehensive price monitoring system with mandatory price negotiations system, if necessary.[46]

All drugs in the National List of Essential Medicines (NLEM) 2003 would form the basis of drugs for price control/monitoring.

What will be the principle of price regulation? To quote from the Report's Executive Summary:

> The Task Force recommends that the National List of Essential Medicines (NLEM) 2003 should form the basis of drugs for price control/monitoring. To support the process the Government should announce the ceiling price of all drugs contained in the NLEM on the basis of the weighted average price of the top three brands by value of single ingredient formulations prevailing in the market as on 1.4.2005. In cases where there are less than three brands, the average of all existing brands would be taken. The ORG-IMS data can be used for this purpose initially with a retail margin of 20%. For drugs, which are not reflected in ORG-IMS data, the NPPA should prepare the necessary information based on market data collection. In the case of formulations, which involve

> a combination of more than one drug in the NLEM, the ceiling price would be the weighted average of the applicable ceiling prices of its constituents. Excise duty should continue to be payable on the actual MRP of the individual medicines. In the case of drugs not contained in the NLEM, intensive monitoring should be carried out. For any new formulations based on existing APIs (Active Pharmaceutical Ingredients), manufacturer concerned would be required to submit its intended price along with application for marketing approval to the regulator, which would be granted only if the indicated price is consistent with relevant ceiling price. The NLEM should be revised every three years.

This means a) all drugs in NLEM, about 350 in number, would be subject to price control and b) that any combination drug, the bane of India's retail pharma market, would also attract ceiling prices and in fact would be the same as the ceiling price of the NLEM drug. This particular recommendation has the potential of minimizing a great deal of unnecessary and unscientific combinations. (Recommendation 5.8: "For formulations containing a combination of a drug in the NLEM and any other drug, the ceiling price applicable to the essential drug would be made applicable. However, the company would be free to approach the price negotiations committee for a relaxation of the price on the basis of evidence proving superior therapeutic effectiveness for particular disease conditions.")

The method of determining ceiling price if it were left only to the average of top-selling three brands of a drug would have been of course disastrous. Recommendation 5.9 adds the concept of benchmark price: "In order to determine the reasonableness of the ceiling prices fixed as above, the L1 prices quoted in bulk procurement by Government and other designated agencies may be examined for use, provided that the system of bulk procurement meets certain minimum prescribed standards. Recognising that retail distribution has costs not reflected in bulk procurement, a mark up of 100 per cent over this reference price is recommended." Elsewhere in Chapter 3, Section 3.2 on "Alternative System of Price Regulation", the Report says:

> Until such time there is reasonable assurance that the bulk price systems are reliable and reflect quality drugs, such benchmarking should not be used or should be confined only to such bulk purchases which meet certain minimum standards for tender procedures."

The first half of the last sentence is a bit of escape hatch. However if the government were serious they could straightaway use the L1 (lowest quotes) prices of say well-run procurement systems like the Tamil Nadu Medical Services Corporation and the Delhi State government and a few others and determine benchmarking prices. At least we hope this is what is meant by "such benchmarking … should be confined only to such bulk purchases which meet certain minimum standards for tender procedures." Recommendation 5.4 adds, "During the transition period (i.e. till the time ceiling prices are fixed and notified) prices of all essential drugs may be frozen.

3.3 Report of the National Commission on Macroeconomics and Health

During September 2005 another important Government appointed commission gave its report. Among other things it observed that:[47]

> … Ten of the top 25 drugs sold in India are non-essential, irrational or hazardous. The market for drugs is highly concentrated with implications on price setting.

Price of drugs

Only 76 drugs accounting for around one-fourth of the drug market are under price control. An examination of the price trends of 152 drugs (consisting of 360 formulations) reveals that antibiotics, anti-tuberculosis and anti-malarial drugs, and drugs for cardiac disorders, etc. registered price increases from 1%-15% per annum during 1976-2000. Indian households spend 50% of their total health expenditures on drugs and medicines. Reducing this burden and ensuring access can be achieved by: (i) bringing all drugs under price control to ensure lower prices for the households; (ii) streamlining and putting in place a system of centralized pooled procurement of drugs so that the public health system can save almost 30% to 40% on costs; (iii) weeding out irrational drugs and irrational combination drugs; and (iv) encouraging ISM drugs for treating diseases for which efficacious and low-cost drugs are available. Price control, as is the practice in several countries such as Canada, is justified on the basis of the drug prices outstripping WPI (Wholesale Price Index). Second, this will address about 90% of the health needs of the community and reduce household spending on these services. Price control should not be limited to essential drugs as the industry can then simply switch its production to the non-controlled categories, depriving people of access to essential drugs ...

Access to affordable drugs[48]

It is difficult to predict the impact of the Patent Act on the access to drugs, both in terms of price as well as availability. At the time of the writing of this report, there are various scenarios emerging, ranging from cautious optimism to downright pessimism. Given the agreed position on the necessity to ensure that we safeguard this basic and fundamental right to access to essential medicines, there is need to carefully study experiences of other countries and coping strategies from the patients' and not only the commercial point of view. We see the Government's role to be very critical in being able to exploit the strengths and minimize the threats that are inherent in this Act.

- Expand price control of all drugs and mandate use of only generic drugs in all publicly funded programmes. Such price caps will help contain costs.
- Weed out irrational drugs and irrational combination drugs to substantially reduce household drug expenditures.
- A minimum VAT of 1% as against the proposed 4% should be levied for essential drugs
- Fix ceilings on trade margins as suggested by the interim report of the Sandhu Committee.
- Centralized pooled procurement reduces government expenditure by over 30%-50%. For this, we recommend adoption of the TNMSC model throughout the country.
- The recommendations of the Mashelkar Committee regarding setting-up of the National Drug Authority (NDA) with an autonomous status to take up the functions of drug pricing, quality, clinical trials, etc. need to be implemented without delay. Consequently, the present National Pharmaceutical Pricing Authority (NPPA) could be merged with the proposed NDA and Central Government provide assistance to states for strengthening the drug regulatory system.
- The Patent Act passed recently needs to clarify the scope of patentability; 'reasonableness' of royalty to be paid on the issuance of compulsory licensing; definition of 'significant' for the Indian companies manufacturing these drugs, mechanisms for automatic compulsory licensing and strengthening of the regulatory bodies ...

While the mainstream drug industry in India has opposed the recommendations, it is hoped that the Government of India will at least actively implement the recommendations of its own Commissions and Task Forces.

4. How Much do Drug Formulations Actually Cost and can Cost

We discussed in Section 3 in this chapter, and in Chapter 6, the validity of claims of drug companies that prices are high because of R &D. But let us take the prices of bulk drugs or APIs (Active Pharmaceutical Ingredients) available in the Indian market and calculate the costs of formulations based on these APIs. We show two such calculations. One exercise (Table 10) is the cost of paracetamol tablets from the manufacturing experience of the not-for profit group, LOCOST based at Vadodara, India. In the second (Table 11) we apply the norms given by the Government of India's National Pharmaceutical Pricing Authority (NPPA), with a 100 percent post-manufacturing mark-up. Comparisons with retail market prices show the extent of overpricing.[49] Comparisons with procurement prices of TNMSC (available at <www.tnmsc.com>) will further show the extent of overpricing.

Table 10: Costing of Paracetamol Tablets

	Quantity required per batch in kgs	**Value in Rs.**
RAW MATERIAL COST - Paracetamol	75.000	13480.00
EXCIPIENT COSTS		1016.00
TOTAL RAW MATERIAL COST[1]	(A)	14496.00
MANUFACTURING COSTS		
Labour Cost		1200.00
Electricity Cost		1500.00
Packing Material Cost		1250.00
Testing Charges		1500.00
TOTAL MANUFACTURING COSTS	(B)	5450.00
TOTAL COST	(A) + (B)	19946.00
TOTAL COST PER 1000 TABS		135.70
Assessable Value		176.40
Excise		12.24
Selling Price		188.64
MRP PER 1000 TABS		234

[1] That is the total Raw Material Cost per 1000 tablets = Rs 14,496 / 150 = Rs 96.64. Costs as of Dec 2004.

Table 11: Pricing of Drugs not in Price Control as Per DPCO & NPPA Costing Norms*						
Name	**Use**	**Selling Price after 100 % mark up per 10 Tabs/ Caps ***	**Present MRP in market of a similar product**	**Brand Name of similar product**	**Name of Manu-facturer**	**% of MRP to 100 % MAPE price**
1	**2**	**3**	**4**	**5**	**6**	**7**
Acyclovir Tabs 800 mg	Antiviral useful in AIDS, herpes, etc.	106.24	187	Acivir DT	CIPLA	176
Albendazole Tabs 400 mg	For treatment of worms	11.38	123.70	Combantrin - A	Pfizer	1087
Amlodipine Tabs 5 mg	For High Blood Pressure	2.14	51.52	Amloguard	Pfizer	2407
Amoxycillin Caps 250 mg	Antibiotic	16.48	59.50	Twicyl	Bio-Evans	361
Atenolol Tabs 50 mg	Myocardial Infarction, High BP, Angina.	3.04	22.14	Atenova	Lupin	727
Cephalexin Caps 500 mg	Antibiotic	54.13	129.00	Ceff	Lupin	238
Cetrizine Tabs 10 mg	Anti-allergic	1.74	30.00	Cetrizet	Sun	1719
Diazepam Tabs 5 mg	Sedative	3.22	14.00	Calmpose	Ranbaxy	435
Enalapril Maleate Tabs 5mg	Antihypertensive, for Congestive Heart failure and other Cardiac conditions	2.03	19.00	Nuril	US Vitamins	936
Ethambutol Tabs 800mg	Anti-TB, Anti-Leprosy	21.18	39.60	Mycobutol	Cadila	187
Fluconazole Caps 150mg	Anti-fungal, also used as an adjunctive in	28.15	106.88	Alfucoz	Alembic	380
Glibenclamide Tabs 5mg	AIDS treatment Anti-diabetic	1.44	6.60	Daonil	Aventis	458
Hydrochlorothiazide Tabs 25	Diuretic	1.73	15.00	Hydride	Micro Lab	868
Indomethacin Caps 25 mg	Rheumatoid Arthritis,	5.68	14.90	Artisid	Sun	262

Name	Use	Selling Price after 100 % mark up per 10 Tabs/ Caps *	Present MRP in market of a similar product	Brand Name of similar product	Name of Manu-facturer	% of MRP to 100 % MAPE price
1	2	3	4	5	6	7
Isoniazid Tabs 300 mg	Anti-TB.	306.00 per Bulk pack of 1000 Tabs	795.24 per Bulk pack of 1000 Tabs	Isonex	Pfizer	260
Mebendazole Tabs	For treatment of worms	2.70	6.00	Mebazole	Torrent	222
Metformin HCl Tabs 500mg (S)	Anti-diabetic	4.28	7.70	Baymet	Bayer	180
Metoclopramide Tabs 10 mg	Anti-vomitting	1.80	8.90	Perinorm	IPCA	495
Ofloxacin Tabs 400 mg	Antibiotic	38.93	96.00	Floxur	Merind	247
Paracetamol Tabs	For Fever, Pain	3.27	7.50	Calpol	GSK	230
Pyrazinamide Tabs. 750 mg	Anti-TB.	17.94	44.40	PZA-CIBA	Novartis	248
Roxithromycin Tabs 150 mg	Antibiotic	28.68	85.00	Zerox	Ozone	296

* This work sheet prepared by T.Srikrishna gives estimated prices of a sample range of commonly used drugs currently not under Price Control. The estimated prices are costed using DPCO NPPA norms of conversion, packing and losses. Column 7 gives the extent to which prices in the market are above DPCO norms if the latter were applicable. For example, Amloguard by Pfizer is priced 24.07 times what would have been its price if it were under price control. Drug prices of leading brands from *Drugs Today*, July-Sep 2003. and *MIMS India*, July 2003. NPPA norms have changed since, but the argument stands.

Annexure1

Pricing and Price Control of Drugs and Pharmaceuticals[50]

…. 6.10 While replying the specific query of the Committee about the drug price control systems in other countries, the Department of Chemicals and Petrochemicals submitted the following details in a written note: -

"Price control in one or other form is exercised in all the countries. In the developed countries it is exercised through reimbursement scheme and through Insurance Scheme. The feature of the various methods used are as follows: -

(a) Cost Plus
The Cost plus method bases permitted rise on the cost of production, allowance being made for marketing and R&D expenditure. The low ratio of direct cost to total cost in the pharmaceutical industry makes the cost plus pricing method potentially a difficult technique to apply without any bias.

(b) Internal Comparison
In this system prices are fixed by reference to comparable drugs already on the national market, concessions being made to innovative products with therapeutic advantages. This means that similar products will be similarly priced leaving little room for price competition. In this system the prescribing freedom of the Doctors is not compromised. The prices of new drugs in which there is no equivalent on the national market may be determined by using the price in another country. Spain, Luxembourg and Portugal follow this system.

(c) External Comparison
In external comparison the price of a particular medicine in other countries is taken as the standard. In Ireland, for example, external comparison is used by linking local prices to a Five country formula.

In most of the member states of the European Community, pharmaceutical expenditure is also controlled by one means or the other. Two principal ways of curbing expenditure is by reimbursement control or cost containment. The methodologies used are as under: -

(a) Positive List
A positive list contains those drugs for which reimbursement is being made partly or wholly by the Government. In countries with product-by-product price control, a positive list is a integral part of the price control.

(b) Negative List
A negative list is a list of those drugs which are not reimbursed at all. An inclusion of any drug under this list automatically results in non-prescription of this drug.

(c) Reference Prices
In this method the reimbursement limit for a group of identical or equivalent products is fixed. Reimbursement is made only on the basis of the reference price and any higher price has to be borne by the patient.

(d) Volume related price
Under this method, practiced in France, in order to tackle new mega priced drugs, a sales volume is fixed. Should actual sales exceed the forecast sales volume, the price will have to be reduced through negotiations between the authorities and the manufacturer.

(e) Promotional Expenditure Control
Through this method an attempt is made to keep the promotional expenditure under control either by imposing a tax on such expenditure or by restricting the amount that can be spent on promotion expenditure.

(f) Transfer to OTC status
This is an alternate to the negative list because one a drug is specified as an OTC drug, the consumer has to meet the entire cost.

(g) Economical prescribing habits
In some countries the authorities have tried to promote economical prescribing habit in order to encourage pricing of cheap, safe and effective drugs. This is achieved buy publishing an essential drug list or by prescribing disincentives for Doctors who are found to be exceeding the average price for drugs prescribed.

(h) Percentage of co-payment
In a number of EC countries, the patient is obliged to pay a percentage of the cost of the drugs prescribed. In some countries the percentage is linked to the financial and medical condition of the patient.

6.11 The Department has submitted a statement showing the drug price control systems in European countries as under:

Country	Individual drug Price control	Basis
Belgium	Yes	Internal comparison (cost plus)
Denmark	No	Reimbursement control-reference price system
France	Yes	Internal comparison
Germany	No	Reimbursement control-reference price system
Greece	Yes	Cost-plus for locally produced, external comparison for new drugs.
Ireland	Yes	External comparison
Italy	Yes	Internal comparison (cost-plus)
Luxembourg	Yes	External comparison (Belgium)
Netherlands	Yes	Reimbursement control-reference price system
Portugal	Yes	External comparison
Spain	Yes	External comparison but control of profit Company-by-company
U.K.	No	Rate of return fixed company-by-company Through negotiations with the D/o Health, UK
Austria	Yes	External comparison, (cost-plus)
Finland	Yes	External comparison, (cost-plus)
Sweden	Yes	External comparison, (cost-plus) profit margins
Spain	Yes	External comparison but control of profit Company-by-company
U.K.No		Rate of return fixed company-by-company Through negotiations with the D/o Health, UK
Austria Yes		External comparison, (cost-plus)
Finland	Yes	External comparison, (cost-plus)
Sweden	Yes	External comparison, (cost-plus) profit margins

6.11 While analyzing some prominent pricing system, the Department submitted the following details:

"The Japanese drug pricing system has to be viewed in the background of the existing medical insurance system. The National Health Insurance Drug Price list is an itemized list of pharmaceutical products which can be used for insurance of medical care. Based on surveys the list is revised periodically. The list contains approximately 13,500 drugs and the Drug Price Calculation method is laid down by the Chuikyo (The Central Social Insurance Medical Council).

China follows the cost plus system for fixing prices of drugs. The State Administration or Prices analyses the cost of production of a particular drug as conveyed by the factory which manufactures it and adds an acceptable level of profit margin to it to arrive at a fair price. This fair price is conveyed to the State Administration of Pharmaceuticals and to the sub-office of the State Administration of Pharmaceuticals, who specifically deal with the price of a drug. The official price of each drug is finalized after the approval has been obtained form the State Administration of Pharmaceuticals which is an independent office under the State Council.,

Canada has set up the Patented Medicine Prices Review Board which ensures that the prices of patented medicines are not excessive. The board is an independent autonomous and quasi-judicial body and the Government has no power to direct it. The board determines if the price is excessive by applying the reasonable relationship test, the therapeutic class comparison test, the international prices comparison test or by comparing the change in prices with the change in the consumer price index over a specified period"

Endnotes

[1] Parts of this chapter are updated and revised from chapters/articles published earlier in the *State of India's Health Services Report*, 2004, CEHAT, Mumbai; *Impoverishing the Poor: Pharmaceuticals and the Drug Pricing in India*, LOCOST/JSS, 2004; and *Combat Law,* October 2005.

[2] The Reserve bank of India (RBI) Rural Indebtedness survey of late eighties showed that amongst non-production loans healthcare was the first reason and amongst all loans it was the 2nd reason for indebtedness. The 52nd NSS Round on morbidity, utilizations and expenditure records indebtedness due to hospitalization. NSS 42nd and 52nd round and various other surveys show that between 15-40% of reported morbidities were unattended because of economic reasons. The Rural Labour Enquiry Report On General Characteristics Of Rural Labour Households (55th Round Of N.S.S.) 1999-2000 shows that men (women) on the average worked for 222 (122) wage days in a year and lost 31 (77) days in a year due to sickness. See <http://labourbureau.nic.in/RLE992k%20GenChar%20Annex%20I.htm>. The average earnings for all households for men ranged from Rs 40 to Rs 54 (Rs 28 to Rs 34 for women) and at least 25 percent of rural households were indebted at any point of time.

[3] See for instance, *Report of the National Commission on Macroeconomics and Health*, New Delhi, Sep 2005.

[4] The corruption has not gone but it is probably less even as functionaries of the State find newer and newer ways of rent collection. Even today getting new drug approvals and licenses entails palm greasing for most. The fact irrational and hazardous drugs continue to exist is probably another source of corruption. It is also in the interest of contract research organizations and many Pharma manufacturers and retailers to keep a lax State lax.

[5] But reforms are now getting a more "balanced" tone. With the State, or at least sections of it, realizing that there is no alternative for the State but to actively shape the content of health services.

[6] The pricing part of the policy that would lead to further decontrol has been stayed by the Karnataka High Court; the matter is now in the Supreme Court pending appeal by the Government of India. For a critique of the Pharmaceutical

Policy 2002, see Chapter 1 of LOCOST/JSS 2004, "Missing the Woods for the Trees: Drug Price Control and Pharmaceutical Policy 2002".

[7] Report of the *Drug Price Control Review Committee*, Dept of Chemicals and Petrochemicals, New Delhi, October 1999. Hereafter *DPCRC Report*, 1999.

[8] See even more recently, "Price control to be brought down to 35 drugs in Pharma policy 2005, monitoring on 319 others", Friday, November 25, 2005, at <www.pharmabiz.com>. As of going to the press, Jan 2006, a draft policy is in circulation for comments available at the NPPA website.

[9] AIDAN and ors. Versus Union of India in the Supreme Court of India WP (Civil) 423/ 2003). See also for arguments of the case summarized in *Impoverishing the Poor: Pharmaceuticals and Drug Pricing in India,* LOCOST/JSS, Baroda/Bilaspur, December 2004. Hereafter LOCOST/JSS 2004.

[10] The price control on drugs of any category is partial at best, with only one or two drugs of a category of drugs being represented in the price controlled list. For example, in the case of NSAIDs only ibuprofen, aspirin, and phenylbutazone are represented in the previous DPCO list while in the market under the category of NSAIDs, 21 drugs are available. This partial representation of drug categories seriously dilute the efficacy of the DPCO in making essential drugs available to people, especially by shifting demand away from a price-controlled drug to those alternative drugs not under price control.

[11] Out of the top 300 top selling brands only 115 brands were of drugs, which are included in the National List of Essential Medicines 2003; i.e. 62% of brands were of drugs, which were not considered relevant by experts to be included in the National List of Essential Medicines (2003). These include more expensive alternatives of essential drugs, irrational combinations, and irrational drugs.

[12] For National Health Policy (NHP), see <http://mohfw.nic.in/np2002.htm>

[13] See Bhargava, Anurag in 'Pharmaceutical Policy (PP)2002 and National Health Policy (NHP) 2002: Discordance in Perspectives and Content', in LOCOST/JSS 2004, op.cit.

[14] *Surviving the Pharmaceutical Jungle* by Nobhojit Roy and Neha Madhiwalla is a new WHO funded study on the unethical promotional practices of pharma companies in India. Jan-Mar 2004 *Issues in Medical Ethics.* For the study see <www.issuesinmedicalethics.org/docs/Pharmrpt.pdf>

[15] See for example the article "Continuing Rise in Drug Prices- Brand Leaders Show the Way" by Wishvas Rane, *Economic and Political Weekly*, July 24-30, 1999 at <http://www.epw.org.in/showArticles.php?root=1999&leaf=07&filename=352&filetype=html>
Also see Rane's "Have Drug Prices Fallen?", *Economic and Political Weekly,* November 1 , 2003 at <http://www.epw.org.in/showArticles.php?root=2003&leaf=11&filename=6439&filetype=pdf>

[16] See Chapter 4 in LOCOST/JSS 2004, "Pharma Pricing in India: a failure of the Market(s)?"

[17] Source for box, "There is No other…": Bhargava, et al in LOCOST/JSS 2004, Chapter 2, "Anarchy in Retail Drug Prices in India."

[18] See for detailed discussion: Bhargava, Anurag. "Price Control Policy and Public Health: Irrelevance and Danger of Applying only Economic Criteria", in LOCOST/JSS 2004, op.cit.

[19] See also Srinivasan, S. "How Many Aspirins to the Rupee? Runaway Drug Prices",*Economic and Political Weekly*, *February 27-March 5, 1999* at <http://www.epw.org.in/showArticles.php?root=1999&leaf=02&filename=108&filetype=html>
See also <http://www.tnmsc.com/l1rate0304.doc> for latest tender procurement prices of the Govt of Tamil Nadu.

[20] Tender prices of the Tamil Nadu Medical Services Corporation (TNMSC) at <www.tnmsc.com>.

[21] See Bhargava, et al in LOCOST/JSS 2004, Chapter 2, "Anarchy in Retail Drug Prices in India". Typically a way of justification of these differential prices by those who see this as evidence of markets at work runs somewhat like this: "Manufacturers offer discounts on brand-name drugs based on both volume and the purchaser's ability to influence market share by systematically favoring one brand-name drug over another … The more influence the purchaser wields in his ability to favor one brand-name drug over a similar competing drug, the higher the discounts and rebates can be. In a sense, this is price competition at work. Differences in price result because manufacturers apply typical profit-maximizing strategies based on the price sensitivity of buyers. According to economic theory, no purchaser pays a higher price to

make up for the discounts offered to somebody else. Instead, each pays the price dictated by his or her price sensitivity." Quoted in "Why Different Purchasers Pay Different Prices for Prescription Drugs" by Anna Cook, Ph.D. , Mathematic Policy Research, Inc. A memorandum prepared for the Department of Health and Human Services, Conference on Pharmaceutical Pricing Practices, Utilization and Costs, August 8-9, 2000, Leavey Conference Center, Georgetown University Washington, DC.

[22] V.Roy, S. Rewari (1998). "Ambiguous Drug Pricing: A Physician's Dilemma". *Indian Journal of Pharmacology*,30: 404-407.

[23] See Anurag Bhargava, Smita Khobragade and Meenakshi Jambulkar,. "Anarchy in Retail Drug Prices in India," Chapter 2 of *Impoverishing the Poor,* op.cit.

[24] P A Francis. "High Profiteering in Generics." *Pharmabiz,* Editorial, September 20, 2000.

[25] Source: Anurag Bhargava. "Anomalies In Drug Pricing and Sale of Drugs." Chapter 11 of *Impoverishing the Poor,* op.cit.

[26] Reproduced from Chandra Gulhati. "Drug Price Control: Principles, Problems and Prospects." Chapter 3 of *Impoverishing thePoor,* op.cit

[27] According to the Mashelkar Committee Report: "From the information conveyed by the States, it is observed that there are 418411 total number of sales licenses including 253666 retail licenses and 145447 wholesale licenses and a combined figure of 19298 retail and wholesale licences given by Karnataka. This total number is not absolute because majority of the sales units have both retail as well as wholesales licenses. Currently, there are 935 Drug Inspectors in all States/UT's in the country put together. Presuming that the number of sales units to be inspected will be approximately 300,000, the number of Drugs Inspectors required is estimated to be 1500."

[28] 'Drug Firms' Incentives Fuel Abuse by Pharmacists in India', Daniel Pearl and Steve Stecklow in *The Wall Street Journal*, August 16, 2001.

[29] Details are in *Impoverishing the Poor: Pharmaceuticals and Drug Pricing in India,* LOCOST/JSS, Baroda/Bilaspur, December 2004.

[30] Shobana R Etal. *Diab.Res.Clin.Prac* 2000. 48; 37-42.

[31] Shobana R etal. *Diab.Res.Clin.Prac* 2002. 55; 45-48.

[32] "Prices Of Most Popular Drugs For Seniors Rose Nearly Three-And-One-Half Times The Rate Of Inflation Last Year -- Prices Of 27 Of The Top 50 Drugs Sold To Seniors Rose More Than Three Times The Rate Of Inflation" at /www.familiesusa.org/site/PageServer?pagename=Media_Out_of_Bounds, July 9, 2003

[33] See <http://www.familiesusa.org/site/DocServer/Going_without_report.pdf?docID=273>

[34] See <http://www.doh.gov.uk/pprs/index.htm>

[35] Information can be obtained from the following websites about medicine pricing policies in different countries.
Medicine Policy in Netherlands:
<http://www.netherlands-embassy.org/article.asp?articleref=AR00000251EN>
Pharmaceutical Benefits Pricing Authority (Australia):
<http://www.health.gov.au/pbs/general/pricing/pbparpt.htm>
Patent Medicine review Board sets the medicine prices in Canada:.
<http://www.pmprb-cepmb.gc.ca/english/home.asp?x=1>

The European Commission website, <http://pharmacos.eudra.org/>, has information about pricing policies of a number of countries including France, Germany, Sweden, United Kingdom. Following are some other websites:

The Netherlands Pharmaceutical Pricing and Reimbursement Policies:
<http://pharmacos.eudra.org/F3/g10/docs/tse/Netherlands.pdf>
Australia: <http://pharmacos.eudra.org/F3/g10/docs/tse/Australia.pdf>
New Zealand Pharmaceutical Pricing and Reimbursement Policies:
<http://pharmacos.eudra.org/F3/g10/docs/tse/NewZealand.pdf>
Finland Pharmaceutical Pricing and Reimbursement Policies:
<http://pharmacos.eudra.org/F3/g10/docs/tse/Finland.pdf>

Sweden:
<http://pharmacos.eudra.org/F3/g10/docs/tse/Sweden.pdf>
WHO website on drug prices:
<http://www.who.int/medicines/organization/par/ipc/drugpriceinfo.shtml>

[36] "Yet, government-imposed price and market access controls serve as a barrier to trade that diminish or eliminate the very incentives that lead to the continued development of innovative and safe pharmaceutical products, while inhibiting or preventing patient access to the latest pharmaceutical innovations. Moreover, those controls deny American firms and workers the ability to compete on fair and equitable terms in foreign markets and undercut the value of intellectual property rights." For full submission see, PhRMA "Special 301" Submission Appendix C, "U.S. Government Needs To Take Action To Address Foreign Price Controls" at <http://www.phrma.org/international/Appendix_C_Market_Access.pdf>.

[37] "Critique of the DiMasi/Tufts Methodology and Other Key Prescription Drug R&D Issues" at <http://www.citizen.org>. See also at the same website "America's Other Drug Problem: A Briefing Book on the Rx Drug Debate" and "Rx R&D Myths: The Case Against The Drug Industry's R&D 'Scare Card' ".

[38] DiMasi, J. A., R. W. Hansen, and H. Grabowski. 2003. "The price of innovation: new estimates of drug development costs". *Journal of Health Economics* 22:151-185. And an earlier one: DiMasi, J. A., R. W. Hansen, H. G. Grabowski, and L. Lasagna. 1991. "Cost of innovation in the pharmaceutical industry". *Journal Of Health Economics* 10:107-142.

[39] See *The Truth About the Drug Companies: How they deceive us and what to do about it.* Marcia Angell. . Random House, 2004. .

[40] See for instance "The Benefits of Medical Research and the Role of NIH" at <http://www.meduohio.edu/research/nih_research_benefits.pdf>.

[41] Quoted in "The Benefits of Medical Research and the Role of NIH", op.cit., page 35

[42] For a brief discussion see the Chapter on Patents.

[43] Anagha Pradhan, Renu Khanna, Korrie de Koning and Usha Ubale in "Quality Assurance in a Public Health System: Experiences of Women Centred Health Project, Mumbai, India", SAHAJ, Baroda, 2004

[44] Anagha Pradhan, et al, op.cit.

[45] See: S.Srinivasan and T.Srikrishna. "Making Available Life-saving Drugs at Reasonable Prices: the Task Force Report". *EPW*, October a8, 2005

[46] Quoted from: "The Strategic Approach", Executive Summary of the Report.

[47] Executive Summary of the *Report of the National Commission on Macroeconomics and Health*, Government of India.

[48] Recommendations of the *Report of the National Commission on Macroeconomics and Health*, Government of India.

[49] See also Chapters 8 and 9, *Impoverishing the Poor* for more details.

[50] Extract from Chapter VI of *Report on Pricing and Availability of Drugs/Pharmaceuticals*, Ministry of Chemicals and Fertilisers (Dept of Chemicals and Petrochemicals), 15th Report of the Standing Committee on Petroleum and Chemicals (August 2001), Thirteenth Lok Sabha , Lok Sabha Secretariat, New Delhi.

Chapter 8

Women and Medicines[i]

1. Medicines and Women's Health

Health care and health services for women continue to be neglected areas. Except during childbearing or for contraception, women in India hardly access the health care system. Besides, the "culture of silence" regarding health problems and lack of autonomy in decisions about their own health,[1] family funds allocated to clinic visits and medicines are limited and women themselves tend to neglect their health, according it least priority. In families, there is often gender discrimination as to who gets health care as a priority. After dowry, medical care is the second major cause of rural indebtedness in the country.

Women and men suffer differential risks with respect to various diseases. (See box below on *Men, Women, and Disease Risk*.) Differences in pharmacokinetics, pharmacodynamics, and physiology contribute to the phenomenon that women and men frequently respond differently to drugs. Hormonal influences, in addition, play an important role.

Medicines (or drugs) specially affect women in special ways: drugs have effects on the reproductive system, especially during pregnancy and lactation. Drugs affect the foetus in many known and unknown ways (see section 2.11 and after on Drugs during Pregnancy and Lactation in Chapter1). Drugs also pass through the breast milk and can affect the child. Sometimes some effects of drugs are latent and are visible only after some years either on the woman, or on her child or on the child's progeny. Women metabolise drugs differently than men. There is evidence to show that drug safety data are analysed by gender only in 54 percent of the cases and efficacy was analysed by gender only in 43 percent of the cases.[2] (See also box below on *Women and Men Respond Differently to Pharmaceuticals*.[3])

Secondly, women are targets of provider-centric population control: injectable contraceptives, oral contraceptive pills, hormonal drugs, fertility regulators, IUDs, etc. In addition menopause, menstrual regulators, hormone replacement therapy are post-reproductive uses of drugs about which not much is known on the metabolism of women. Only 12 percent of 53 drugs approved in recent years in the USA had special studies done to look at hormonal interactions or interactions with oral contraceptives.[4]

This needs to be looked in conjunction with the tendency to medicalise pregnancy in even normal cases. Caesarians as well as hysterectomies are becoming commoner by the day and with it unncecessary drug interventions. Again AIDS is an unknown territory and AIDS treatment and clinical research needs far more gender focus than ever (see box below on *Towards Ethical Research for Women Living with AIDS*).

---

[i] Source: *Towards Comprehensive Women's Health Programmes and Policy*, SAHAJ and WAH!, Baroda, 2002, Chapter 29. Adapted and modified version of the chapter on the same theme coauthored by S.Srinivasan and Mira Shiva.

Men, Women, and Disease Risk[5]

Heart attack	Men have more, but women are more likely to die within a year after a heart attack; women tend to get heart disease seven to 10 years later than men
Stroke	Women have fewer strokes, but are more likely to die from them than men; women are generally older than men when they have a stroke
Depression	Twice as common in women
Migraine	Three times more common in women
Hearing loss	More common in men
Nearsightedness (myopia)	More common in women through age 60
Irritable bowel syndrome	More common in women
Cancer	Cancer of the lungs, kidneys, bladder, and pancreas are more common in men; thyroid cancer is more common in women
Osteoporosis	More common in women
Rheumatoid arthritis	Two to three times more common in women
Gout	More common in men
Lupus	Nine times more common in women
Fibromyalgia	Nine times more common in women

Women and Men Respond Differently to Pharmaceuticals

- A much higher percentage of women than men develop the life-threatening ventricular arrhythmia torsades de pointes after taking a variety of drugs, such as antihistamines, antibiotics, anti-malaria drugs, cholesterol lowering drugs and anti-arrhythmia drugs (Ebert et al., Journal of Women's Health 1998;7(5):547-557; Reinoehl et al., American Heart Journal 1996;131(6):1184-1191; Makkar et al., Journal of the American Medical Association, 1993;270(21):2590-2597).
- A liver enzyme, CYP3A4, is responsible for metabolizing more than 50% of pharmaceutical drugs. This enzyme is more active in women than men, which can lead to sex differences in effectiveness and/or adverse reactions (Tanaka, Journal of Clinical Pharmacy and Therapeutics 1999;24(5):339-346; Geiter and Gundert-Remy, European Journal of Drug Metabolism and Pharmacokinetics 1996;21(2):123-128; Harris et al., Drugs 1995;50(2)222-239).
- The anesthetics atracurium and vecuronium affect women and men differently. Women are much more sensitive to the neuromuscular blocking activity of both drugs (Xue et al., Journal of Clinical Anesthesia 1999;11(5):397-405; Xue et al., Anesthesia and Analgesia 1998;86(6):1322-1327; Xue et al., British Journal of Anaesthesia 1998;80(6):720-724).
- Women wake up from anesthesia (combination of propofol, alfentanil, and nitrous oxide) faster than men - an average of 7 minutes for women versus 11 minutes for men (Gan et al., Anesthesiology 1999;90(5),1283-1287).
- Diazepam, a muscle relaxant which is often used to treat epilepsy, impairs the psychomotor skills (control of voluntary movements) of women more than men (Palva, Medical Biology 1985;63(2):92-95).

- Certain types of pain killers, called kappa opiates, are more effective in providing post-operative pain relief in women than in men receiving the same treatment. (Gear et al., Pain 1999;83(2):339-45; Gear et al., Nature Medicine 1996;2(11):1248-50; Gear et al., Neuroscience Letters 1996;205(3):207-209).
- When compared with placebo, ibuprofen is less effective at providing analgesic relief for women than for men during experimentally induced pain situations (Walker and Carmody, Anesthesia and Analgesia 1998;86(6):1257-1262).
- Women are 48% more likely than men to use any abusable prescription drug, possibly because women are more likely to have a regular doctor than men (Simoni-Wastila, Journal of Women's Health & Gender-Based Medicine 2000;9(3):289-297).

Source: <http://www.womens-health.org/justthefacts.html#responses>

Toward Ethical Research for Women Living with AIDS

A National Conference on Women & HIV at Pasadena, USA in May 1997 demanded that:

- The (US) FDA must require the inclusion of women in all phases of clinical research so that meaningful analysis can be done.
- The pharmacokinetics of any drug to be used by women must be assessed in women, and dosing and dose intervals determined accordingly. Without this information, no Phase II studies should be approved.
- Animal fetal toxicity and reproductive studies should be completed before an IND is accepted for Phase I trials. An information bank should exist describing any and all such studies and their findings. If such studies demonstrate fetal toxicity or reproductive genetic problems, women and men should be informed and should be allowed to participate if they wish.
- Pharmaceutical companies with approved anti-HIV and opportunistic infection drugs must complete Phase I studies in women and remaining animal fetal toxicity studies within 1 year.
- New drugs must not be approved unless sponsors present meaningful analyses by gender, including dosing information by gender. Statistical analyses for NDAs cannot be presented for only one gender.
- All previously approved, as well as new anti-HIV treatments and treatments for opportunistic infections must be labeled to indicate whether or not they have been tested in women.
- Women living with HIV/AIDS should be represented in all review committees for INDs and NDAs, and accelerated approvals.

Because drugs are likely to have special effects on women, very often women are not included as subjects in drug studies. Though in fact other than serving as an excuse this should be the very reason for doing gender sensitive research. (See box below on *Women and Clinical Trials*)

Sometimes drugs are wrongly advertised: the case of tamoxifen advertising in the US is a case at point. It had been advertised to imply that the drug is a breast cancer preventive whereas it suppresses the recurrence of breast cancer in cases of early localised disease.

A major public health problem among women and girls in India is iron deficiency anemia. Repeated child births and menstrual blood loss can worsen the anaemia, so also the presence of hookworms, etc. Intake of iron rich foods, e.g., green leafy vegetables, fenugreek, drumstick, cooking in iron vessels help in prevention of anaemia as also iron and folic acid tablets (ferrous sulfate with folic acid). Folic Acid facilitates absorption of iron in severe iron deficiency anaemia and therefore iron and folic acid are given together in pregnancy. But the way drug policy is formulated in India, simple iron and folic acid tablets to treat anemia are not available in the

retail market. Costly and irrational iron tonics are available. (For example the price of iron folic acid tablets is Rs 6.50 per 100 of LOCOST, a public charitable trust manufacturing drugs, whereas Hepasule caps of Biological Evans is Rs 7.40 per 10 ("one cap twice daily after meals"), Iberol 200 ml ("10 ml twice daily") manufactured by Pharmacia is Rs 69 and so on (prices as per *MIMS India*, Oct 2006). Most of these near equivalents have other ingredients which are not usually necessary. Equivalent multivitamin tablets too would not, or should not, cost as much. Even though there has been an anaemia prophylaxis program for decades, nutritional anaemia continues to be a major problem for women contributing to 20% of the maternal mortality.

Women and Clinical Trials

"Historically, health researchers have used male subjects to determine the safety and efficacy of drugs and treatments. Reasons given for the exclusion of women have included difficulty in recruiting and retaining women in clinical trials; concern about the potentially confounding effects of a woman's hormonal changes on the treatment; the desire to protect a potential fetus (regardless of whether a woman intends to conceive); and fear of liability issues if a fetus is harmfully exposed. As a result of these last two reasons, women of childbearing age were systematically excluded from clinical trials until very recently.

"Unfortunately, if a drug is not tested on women, there is no way to know if it is safe or effective for women. If clinical trials do not include women, potential damage to a fetus or the effects of hormone changes on the drug's effectiveness will only be discovered after the drug has been approved and is on the market. The reasons that are given for excluding women from clinical trials are the very reasons why women must be included. Additionally, the discovery of differences between male and female responses to disease and treatments has implications for both genders in clinical practice, disease prevention, and medical education. Studying women could improve treatment for men and women.

"There have been several important milestones in the fight to mandate the inclusion of women in clinical trials:
1986: The National Institutes of Health (NIH) adopted a policy requiring the inclusion of women in clinical trials.
1990: A General Accounting Office report revealed that women were still being excluded. The Physician's Health or "aspirin" study, designed to examine the impact of taking aspirin on cardiovascular disease, was one of many large studies revealed to be excluding women.
1993: The NIH Revitalization Act of 1993 mandated the development of guidelines on the inclusion of women and minorities in clinical trials.
1993: The Food and Drug Administration rescinded earlier guidelines recommending restrictions on the participation of women with child-bearing potential and left the determination of risks and benefits of their inclusion to patients, investigators, and Institutional Review Boards." (Source: www.womens-health.org)

However, one should ask the question how ethical is it to do clinical trials on pregnant women's foetuses just to study the effects of particular treatment regimes. What will happen to non-literate or otherwise uninformed pregnant women in India if they are subject to drug trials without being told of the consequences even though "informed consent" may be obtained on paper. This is worrisome especially as India has become a favoured destination for clinical trials. (See later in the chapter for discussion on India as a destination for clinical trials.)

Questions to Ask

Whenever the doctor prescribes a drug, any drug, for a woman, she must try to get answers to the following from the doctor:

- Is the drug really necessary?
- Are there non-drug alternatives?
- What are the benefits of this drug?
- What are the common, rare, and serious side-effects of this medicine?
- How is it likely to affect pregnancy and lactation?
- Will it interfere with oral contraceptives or other contraceptive methods I am using or likely to use?
- Are there any safer alternatives to this drug?
- Can a small overdose, such as one extra pill, be dangerous?
- Can the prescription interfere with other medications I am taking?
- Does the drug have any serious interactions with other drugs or with a large number of other medications?
- Are there any known and or suspected long-term effects of this drug?
- Does the drug require laboratory monitoring to ensure that I am not being harmed?

And finally, if you experience any side-effects, immediately report them to your doctor.

Do the Side-Effects of AIDS Medications Differ from Men to Women?

That is an excellent question and one we are trying to learn more about. I cannot make a general statement as each drug is different. There is a study suggesting that nevirapine is more likely to cause a rash in women compared with men. This study also suggests that the severity of the rash may be worse in women. Some experts believe that women may experience more gastrointestinal side-effects with the protease inhibitors. Some of this may be due to the fact that in general, women weigh less than men and possibily that women are given a higher dose of medication then they need. This is one of the reasons why therapeutic drug monitoring may be useful. If we can define the levels of the drug needed, we may be able to measure that drug and adjust the dose based on the actual drug level. It is plausible that individuals experience side-effects of medications because the level of drug is too high. An example of this is indinavir associated kidney stones. There are some studies in development and progress correlating the levels of indinavir with the development of kidney stones. Hopefully, we will have some answers soon.
Unfortunately, many of the initial clinical trials included very few women so we do not have good data on the differences between men and women pertaining to drug side-effects.

Judith A.Aberg, M.D., Washington University, St.Louis, School of Medicine, posted Dec 18, 2001 at
<http://www.thebody.com/Forums/AIDS/Women/Archive/WomenSideEffects/Q98672.html>

2. Misuse of Drugs and its Effects on Women

As we pointed out above, most medicines have effects on pregnancy and breast milk and in some cases, are known to cause congenital malformation of the unborn baby. Women, especially if not literate are more likely to trust their doctors, and are more likely to use these drugs that can cause damage to the child in the womb. (See also box above on *Questions to Ask*). So little drug research takes place with women in mind, that it is difficult to say in advance whether a drug will have specific side-effects in women (see box above on *Do the side-effects of AIDS medications differ from men to women?*).

Some notorious drugs over the years involving women and children have been: thalidomide, diethyl stillbaestrol (DES), EP drugs, and injectable contraceptives and implants like norplant, net-en, depoprovera and quinacrine.[6]

2.1 Thalidomide

Thalidomide first marketed in November 1956 was used for a wide range of conditions ranging from influenza, disorders of the stomach and gall bladder, mild depression, insomnia, and menstrual tension. It was used in the UK as a tranquiliser and sleeping pill. Thalidomide, originally discovered in 1954 by a former Nazi medical officer who worked for the German company Chemie Grunenthal was, 'a drug in search of a disease'. Corrupt, greedy government regulators and corporations allowed the drug, thalidomide, to become the largest over the counter sedative purchased in many European countries. By 1961, when the reports of the drug's side effects were finally being noticed, 64 million thalidomide tablets had been sold. Some 10,000 deformed children were born as result, some dying in the process.[7] Many of the surviving children were without arms or without legs. Some were like limb-less trunks, without either arms or legs.

The story of thalidomide is a grim tale of how a drug was developed and marketed although it lacked a sound safety history and was soon found to have horrific adverse effects, particularly on unborn children. At the same time, thalidomide has undergone a reputation rehabilitation, even approved by the US FDA for specific conditions, and is now hailed as a powerful drug to treat a number of rare and life-threatening illnesses, including for people with multiple myeloma, brain tumors and other cancers, arthritis, lupus, Crohn's disease, multiple sclerosis, leprosy, tuberculosis, and AIDS.[8]

An Uncertain Utopia

Tranquilizers and sleeping pills played a large role in the uncertain Utopia of the 1950s. One doctor testified in Congress that "the people of this nation are being steadily educated by doctors and the drug industry to take a drug whenever they felt anxious about anything." For many people, another testified, drugs were "used as a panacea to solve personal problems." In Great Britain an estimated 1 million people used some type of sedative daily, and about one out of eight National Health Service prescriptions was for sleeping pills. Almost all of the tranquilizers were dangerous barbiturates. Deaths from accidental and deliberate overdose were on the rise; in fact, suicide by sleeping pills was the glamorous way to check out. In 1955, the United States produced almost 4 billion barbiturates, or twenty-six pills for every man, woman, and child in the country. According to Senator Hubert Humphrey, one out of every seven Americans took barbiturates.

The U.S. pharmaceutical industry was now launching over 400 new drugs every year. Prescriptions had nearly quadrupled over the past twenty years, and drug exports had increased twentyfold since World War II. There were pills for everything. Chemists had just announced a drug that could speed up suntanning ("Next summer, something you swallow may turn you the color of a life guard!"); human tests were under way on inmates at Arizona State Prison. The culture was also beginning to learn that some drugs could be very dangerous. In the United States, the "Feds" were beginning to crack down on illegal pep pills like Dexedrine. Long-haul truckers relied on Benzedrine ("bennies" or "co-pilots') to stay awake. There was already a booming black market in these amphetamines at truck stops around the country, and almost anyone could order large quantities of the drug through the mail.

Aldous Huxley was predicting, as he had in both Brave New World and The Doors of Perception that even though most people still relied upon alcohol to forget Communist threats and society's woes, before long a new pill would be

produced to help people unwind. Reconsidering Huxley's fond dream is peculiar today, since we have progressed from "Mother's Little Helper"-by the Rolling Stones-in the sixties to father's little helper-Viagra-in the nineties, and offering a whole smorgasbord of psychotropics, from Prozac to Ecstasy. In June 1956 Huxley wrote an article in the Sunday Times of London, observing that Homo sapiens had been taking mind-altering drugs since prehistory-especially alcohol, of course. "Will the pharmacologist be able to do better than the brewers and distillers?" Huxley wondered. "It seems reasonable to suppose it."

An executive at a British pharmaceutical firm, Distillers Company (Biochemicals) Ltd., read Huxley's article and promptly pointed it out to the company's director, E. G. Gross, in a memo the next day. "The ultimate target," he wrote, "would be the production of the ideal tranquilizing agent to replace alcohol among those people who would prefer to `transform their minds' by this alternative means." Gross replied, ". . . it will not be long before there are as many of these things as there are brands of whisky."

The very same week, Chemie Grunenthal offered Distillers Company an opportunity to license thalidomide for manufacture and distribution in the United Kingdom. From the way it was described by the German company that had invented it, this new sedative was the dream drug for the Utopian market that chemical companies around the world were aiming to conquer. It seemed to the Distillers executives like the answer to their prayers; less than a month after the Huxley article, the company brought quantities of thalidomide back from Germany for testing.

Chemie Grunenthal was another hungry pharmaceutical company, though not yet one of the well-established corporations. Grunenthal was a family-owned business formed in 1946 that initially produced ointments, cough medicines, disinfectants, and herbal medicines in an abandoned, seventeenth-century copper foundry (Kupferhof), built like a fortress out of stone in the small West German village of Stolberg, near Aachen. The closest large city, Dusseldorf, has been called "the desktop of the industrial region" for a century, home to the executive bureaus of coal mines, steel plants, and other heavy industry. Most of the city, apart from the Altstadt, had been heavily bombed and not yet rebuilt when Grunenthal began operations nearby in 1946. In those years, Dusseldorf was not an especially cheerful city. Even today the main boulevard, Heinrich Heine Allee, commemorates the local poet well known to doctors for "Morphine," a poem about Heine's own terrible medical ordeal: "Gutist der schlaf, Der Tod ist besser, Das beste were nie geboren sein." ("Sleep is good, Death is better, The best is never to have been born at all.")

Grunenthal was a subsidiary of a large cosmetics company. Their research was unashamedly market-driven, and their initial corporate strategy was to penetrate the burgeoning antibiotic boom. Conditions in postwar Germany were appalling, and health authorities feared epidemics of tuberculosis and even cholera. So antibiotics were big business for German pharmaceutical companies.

(Excerpted from : Trent Stephens Rock Brynner. *Dark Remedy: The Impact of Thalidomide and its Revival as a Vital Medicine.* Perseus Publishing. 2001.)

2.2 Diethylstilbestrol (DES)

DES, a synthetic estrogen, was given to at least 7 million women in USA, Canada and Western Europe between 1948 and 1971. Initially, no one was sure what it could be given for. It was tried in many clinical conditions but soon came to be given for prevention of miscarriage working on the theory that habitual abortion was caused by a lack of progesterone and could be prevented by giving estrogen that would in turn stimulate the production of progesterone. It was promoted for making normal babies more normal. Clinical trials showed that DES was not only ineffective but it was unsafe. The link between DES and cancer was surmised in 1971. Animal studies way back in the late 1930s and 1940s had shown that DES and estrogens could cause cancer. It also increased chances of abortion. DES daughters are more likely to get carcinogenic abnormalities with 40 percent of the DES daughters likely to have had structural defects in the cervix, vagina, uterus and fallopian tubes. Compared to non-exposed women, DES daughters have four times the risk of miscarriage and pre-term labour. Ectopic

pregnancy, a life-threatening condition, was found to be likely in 4-8 percent of the DES daughters. The complications continued with findings that showed that mothers who took DES had 1.5 times the chance of getting breast cancer, and probably with increased chances for the daughters too.[9]

- "*Diethylstilbestrol (DES), a synthetic estrogen, can cause vaginal cancer in adolescent girls whose mothers took this drug during pregnancy. These girls may later suffer from an abnormal uterine cavity, menstrual problems, a weakened (incompetent) cervix that can cause miscarriages, and an increased risk of having an ectopic pregnancy or having a baby who dies shortly before or after birth. Boys exposed to diethylstilbestrol as fetuses may have penis abnormalities.*" (www.merck.com,home manual).

2.2 High Dose EP Combination Drugs

Around 1982 drug activists in India found that a whole class of high dose Estrogen-Progesterone combination drugs (EP Forte, etc.) were being misused: prescribed by doctors to regularise periods, for pregnancy testing and as abortifacients. The high dose estrogen-progesterone (EP) combination drugs which contain the same female sex hormones as the combined oral contraceptive pill, but at a higher level, were used in the 1950s to regularize missed periods since they were thought to start menstruation in women whose periods were delayed and who were not pregnant. A woman whose periods did not start after taking EP drugs was presumed to be pregnant and hence EP drugs were used for pregnancy testing. But because the drug could apparently bring on menstruation, EP drugs were misused to induce abortion. Although no pharmaceutical company has ever claimed that these drugs will induce abortion, there was evidence in India that they were prescribed by doctors for this purpose and were also sold over the counter for hormonal pregnancy tests. They were being prescribed for endometriosis, functional uterine hemorrhage and menorrhagea. About 20 years later research uncovered evidence that the EP drugs were unreliable as a pregnancy test and ineffective for treatment for missed periods. In fact evidence showed that the drugs were associated with birth defects. Dr. Isabel Gal was the first to show the co-relation between congenital abnormalities and hormonal pregnancy tests and warned about the need to seriously look at use of hormones in pregnancy. For her work she lost her job and was hounded. Yet the withdrawal of these drugs in UK and out of court settlements with some of the pharmaceutical companies were due to her sincere efforts. She also helped with provision of documents in the Public Interest Litigation and the Public Hearings on EP drugs in India. Those women who used this drug for pregnancy testing and continued with their pregnancy exposed their unborn babies to the possibility of birth defects. Cases of birth defect EP children have been documented. Those women who took the drug to induce abortion but did not abort also ran the same risk. These drugs were produced and marketed as safe products, without warning doctors and women against their teratogenic effect. Though many countries had banned them, even as one of the major manufacturers Organon was not even allowed to register or even manufacture the drug in its parent country in Netherlands, these drugs continued to be sold in India. After a relentless campaign running over 6 years for a ban by health and consumer groups, the government of India banned the manufacture and sale of high combination of EP "containing per tablet estrogen content of more than 50 micrograms and of progesterone content of more than 30 milligrams" in 1988. (See also *EP drug* in Annexure, Chapter 4 and VHAI 1988.)

2.2 Other Drugs

There have been several other drugs that are a cause for concern. Over the years there have been a whole slew of drugs whose teratogenic effects have come to be known: anti-cancer drugs, warfarin, anticonvulsants, inhalation anaesthetics, tobacco, alcohol, some psychotropic drugs and barbiturates, tetracyclines, chloremphenicol and some antimicrobial agents and aminoglycosides, antimalarials, antithyroid drugs, corticosteroids, some sympathomimetic drugs, narcotics like morphine, heroin and methadone, and drugs used for premature labour and induced labour. (See Annexure 2 as also *Textbook of Adverse Drug Reactions*, D.M.Davies, ed.OUP, 1981 and after; also chapter on "Drug Use during Pregnancy" in Merck Home Manual at www.merck.com).

* Sales of certain drugs, some in the name of Ayurveda, e.g., 'Select', to allegedly convert girl foetus to boy foetus when taken during pregnancy. Some of these drugs should never have been manufactured in the first place. (The ayurvedic drug Sura with a high alcohol content is another drug that should have not been licensed for production.). Indian market is aflush with numerous aphrodisiacs, the side-effects of which are not well studied.

* Oxytocics like Syntocinon are given to pregnant women to hurry up labour while they are indicated for women who have reached their term but the labour pains have not started. It is being grossly misused for hurrying up labour for the convenience of health care providers while this should be given slowly in intravenous infusion to ensure that the contractions begin as slowly as natural labour pains. It is however being given intramuscularly where the labour contraction get dissipated giving no time for adequate relaxation to the uterine muscles so that nutrition and oxygen supply through the placenta can reach the unborn baby. There have been cases of ruptured uterus and also children being born with birth anoxia resulting in permanent mental retardation and cerebral palsy. In the class of pharmaceutics that are being used only for women, next to female hormones oxytocics have been the second most misused category.

3. Contraceptive Drugs and Women

The efforts under the Government of India's Family Welfare Programme were to increase contraceptive choices. There is also pressure from the manufacturers of these contraceptives and their international lobbies, often giant international NGOs and funding agencies, to "target" these contraceptive "choices" at women. These are however mostly not under the control of the user but are long acting and provider controlled. Research in contraceptive technology continues to be targeted at women: Net En, Norplant, anti-fertility vaccine, RU486. Many of these contraceptives are known to have serious side- effects. In fact all of them require proper screening of women for whom the usage of these contraceptives would be contra-indicated. In cases where pregnancy has not been excluded, long acting hormonal contraceptives are contraindicated. Some of these are contraindicated in cases of women who have irregular menstrual cycle, jaundice, acute or chronic liver disease, hypertension, diabetes, cancer of the breast, uterus or cervix, breast-feeding mothers, women taking anti-TB drugs (these are contraindications mentioned by the makers of Depo-Provera), etc. Some of the side-effects include menstrual disturbances, hormonal imbalance, circulatory and cardio-vascular problems, increased risk of cancer and infertility.

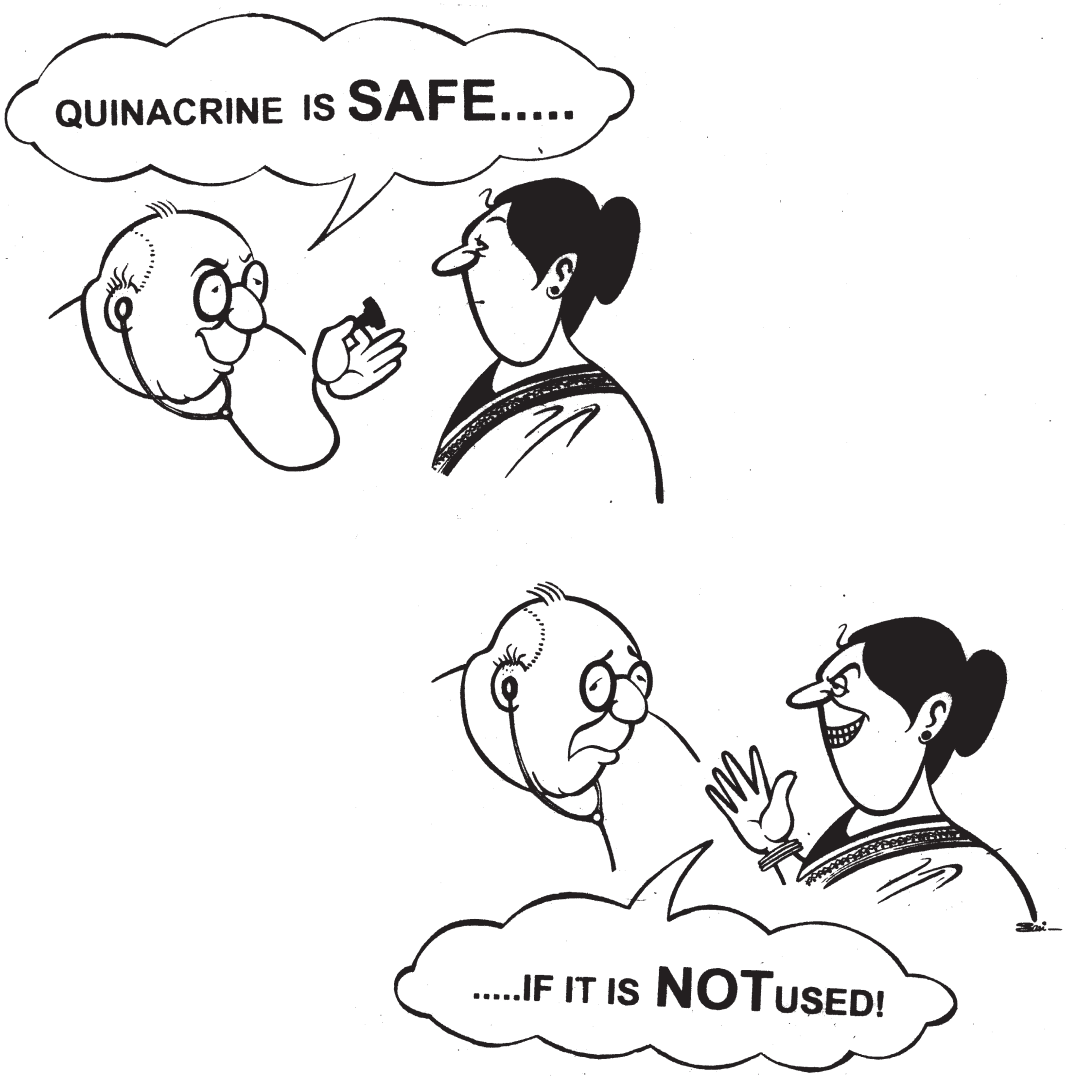
3.1 Quinacrine Sterilisation

Quinacrine is an antimalarial drug. It has been used for permanent sterilsation of women. Quinacrine pellets are inserted into the uterus. They burn and block the tissues at the mouth of the fallopian tubes. The drug has not been adequately tested and has a high failure rate as a contraceptive. Moreover it has serious side-effects like genetic disorders, deformities in future babies in case of failure, risk of cancer, ectopic pregnancy (a condition that can be fatal), menstrual disorders, severe abdominal pain, headaches, backaches, pelvic infection and itching, nervous and genetic disorders, etc.

Trials were carried out on unsuspecting women despite the WHO's recommendation for a cessation of human trials pending further toxicology tests, since initial tests had revealed possibilities of carcinogenicity. In 1992 the Indian Council of Medical Research (ICMR) prematurely terminated its trial due to high rates of failure and complications. However, several private organisations of medical professionals in collusion with drug companies continued to carry out trials with this method of sterilisation. Ironically, the trials were being conducted without any clearance from the Drug Controller of India nor was the ICMR (Indian Council of Medical Research) informed. Quinacrine trials also highlight that there could be several other such clinical trials going on about which the concerned authorities are unaware. As the outcome of an intensive campaign against aggressive promotion of quinacrine sterilsation started by two US-based doctors and their organisation, the International Family Health Association, a public interest litigation was filed within India by, among others, academics and activists from Delhi's Jawaharlal Nehru University (JNU) and the All-India Democratic Women's Association (AIDWA) to ban the use of quinacrine for female sterilisation. In March 1998, the Drug Controller of India gave a written commitment to the Supreme Court that the use of quinacrine for female sterilization would be banned. The Court was also assured that the government, through a gazette notification, "prohibits the manufacture, sale or distribution" of quinacrine in pellet form. Any violation of the order will be punished "with imprisonment for a term which shall not be less than five years, but which may extend to a term of life…and with fine which shall not be less than ten thousand rupees". (Bal et al., 2001.)[10]

3.2 Net En (Norethisterone Enanthate)

Net En is an injectable contraceptive that has both short-term and long-term health effects. It is contraindicated in women with hypertension, diabetes, thromboembolic phenomenon, hepatitis and in pregnancy. Hazards include menstrual chaos, adverse impact on the hypothalamus-pituitary axis in the brain, which could lead to undesirable effects on other systems of the body and systemic disruption. Long-term risks include the possibility of cancer and risk to progeny due to *in utero* exposure. Moreover, return of fertility is not assured. In 1983 and 1984 the ICMR initiated a Phase IV trial of Net En in rural and urban centres to test its acceptability. The Phase IV trials of Net En were conducted in violation of medical ethics without the informed consent of the women who were recruited for the trials. This came to light in 1986 when village women who were attending a family planning camp were injected with Net En even without being informed that they were a part of a trial of an unapproved drug (Bal et al., 2001). This prompted Saheli, Chingari and several other women's groups and individuals to file a writ petition in the Supreme Court of India in 1986 asking for a stay on the Phase IV clinical trials of the Net En. Though the case against Net En was still pending in court, this drug was approved by the Drugs Controller of India for import and marketing



A consumer poster campaign against Quinacrine from Insaf, Mumbai. Quinacrine is an anti-malarial drug, which was being illegally used for permanent sterilisation of women. Quinacrine has several dangerous side-effects. Its use for sterilisation has been banned by the Government of India.

by private practitioners in 1986 and has been officially launched in India for "social marketing" in 1994. The stay order has been since lifted by the courts.

3.3 Depo-Provera (Depo Medroxy Progesterone Acetate)

Depo-Provera is another injectable contraceptive for use by women was initially manufactured by the American multinational, Upjohn. This drug is not allowed for use as contraceptive in USA, but may be prescribed by a doctor after the women gives her informed consent. Yet the drug is sold in third world countries for contraceptive use. The drug is associated with breast and endometrial cancers, osteoporosis, lowered life expectancy and lowered resistance to infection. In addition, the drug causes severe birth defects if a woman who is unaware of her pregnancy takes the drug. The effect of the drug on breast-feeding babies is not well documented, but it could interfere with the babies' normal development and inhibit the transmission of immunities. Despite this knowledge, Pfizer, Depo's then manufacturer and distributor, promoted the drug for nursing mothers because the drug did not stop the flow of breast milk. Depo is also known to cause depression, hair loss, headaches, weight gain/loss, menstrual spotting, heavy bleeding, skin changes, nausea and loss of libido. Earlier trials in Chandigarh in the early 1980s were stopped because of severe bleeding problems. The weight of evidence of the contraceptive is "sufficient to compel its proponents to admit to the injectable's potential for adverse outcomes including death."[11]

The difference between the package insert for the same product given to doctors in US and India were pointed out by women's groups who accused UpJohn of double standards. They also protested about its launching in view of the deteriorating public health services, it was difficult to ensure exclusion of those women for whom injectable hormonal contraceptives were contraindicated and for those who had side-effects and needed follow up. Depo-Provera, was introduced into the Indian market without conducting Phase IV trials which meant that the Indian state conducted no research specific to Indian users before deciding to introduce the drug in the market. The drug dosage was originally designed for the larger, better nourished, healthier western women. It has not been decreased proportionately for the smaller Asian women who are now the target for this drug. Despite the Net En controversy, Depo-Provera was also launched officially, in 1993 for the private market with Max Pharma and in 1994 for "social marketing" (Bal et al., 2001, Saheli 1998, Sama 2000).

The US Food and Drug Administration (USFDA) recently mandated that Depo-Provera carry the "black box" warning label, the agency's most severe warning concerning bone-loss. The warning will reflect the contraindications and also suggest that Depo use should be limited to two years unless other forms of birth control are insufficient. The lax laws in India however, have made it possible for Pfizer to do away with the mandatory 'black-box' warning and the women continue to be unaware about the health risks associated with Depo.[12]

Under pressure from international funding agencies, the Government of India may be keen on introducing these long acting hormonal injectable contraceptives in the National Family Welfare Programme. However, past experience with oral contraceptives and IUDs shows that the health delivery system in India is not equipped for screening women for contraindications, monitoring and follow-up of these women. Moreover, the chances of un-informed or ill-informed use are also high. Women may be administered the drug without their knowledge, or informed only about the convenience to the drugs and not the potential hazards, as was the case in the Phase IV trials of Net En, where women were only told, "take this injection, you won't get pregnant". (Bal et al 2001, Sama 2000, Sathyamala 2000)

3.4 Other Contraceptives

There are other contraceptives like oral pills, IUDs (intra uterine devices) and implants like Norplant which women need to be aware of before using them. The most infamous of these IUDs was the Dalkon Shield and about 2.8 million of them was marketed in the USA in the early seventies. Problems, caused primarily by the tail of the device, led to serious PID (pelvic inflammatory disease) for thousands of women and death at least for 18 women. Several lawsuits and FDA investigations later, Dalkon Shield was withdrawn in June 1974 in USA and even outside USA by March 1975. A trust fund was set up with more than US $ 2300 million to settle the claims. Dalkon Shield spacing was used by many women in India as part of an USAID program. Unfortunately none of the women could seek any claim as they were not informed about it and those who did find out about the claims could not help the women as there were no available medical records.

Some improved versions of IUD (the "loop") have become the standard female barrier method advocated in India's Family Welfare programme. IUDs have severe problems like excessive vaginal bleeding, anemia, etc. and therefore need to be used with caution. Oral contraceptive pills too need to be used with caution and are known to cause havoc with a woman's metabolism.

3.5 Norplant

Norplant is a sub dermal (under the skin) implant. It consists of six match stick sized rubber capsules that release progestin (levonorgestrel) slowly. It is implanted under the skin of a woman's upper arm in a minor surgical procedure using local anaesthesia. The implant prevents pregnancy and was supposed to have been valid for five years.

Norplant 2 and its latest version Norplant R have been opposed by women's groups in India and by others concerned. The opposition has been chiefly because it can be inserted and removed only by doctors and has serious disadvantages ranging from ectopic pregnancy (pregnancy in the fallopian tube) to severe bleeding and even in some cases foetal abnormalities.[13]

The earlier, two-rod version of Norplant (Norplant-2) had already undergone Phase III testing in India. However, the manufacturers were forced to stop producing the silastic material for the rods because of fears of its carcinogenic effect on workers who would be exposed to large quantities of the material. The company stopped production, and attention turned to the six-rod Norplant R made of a different material. In 1992, the ICMR announced Phase IV trials of Norplant R. They argued that the progestin released by the two implants was identical, which meant the results of Phase III trials of Norplant-2 could be applied to the six-capsule Norplant R.

Protests from women's groups followed. They argued that Norplant R was a different device - the drug delivery system was different - and had to undergo safety tests before pre-programme introductory trials. As a result of this pressure, a Phase III trial for Norplant R was designed. The trial depended on the 'cafeteria' approach to select volunteers. Women approaching health services for contraceptive advice were asked to choose after being informed of the various methods available.

Eventually the Government of India abandoned trials and use of Norplant R too owing to public protests.

3.6 Anti-Fertility Vaccines (AFVs)

AFV, an anti-hCG (human chorionic gonadrophin) vaccine, is one of the range of immunological contraceptives that are sought to be introduced.

The vaccine being developed seeks to induce temporary infertility in women by turning the immune system against components in the body which are essential for human reproduction. The human pregnancy hormone HCG is

altered, then coupled to a bacterial or viral carrier so that the immune system mistakes the natural pregnancy hormone for an infectious germ and reacts against it. The body thus does not get a signal to prepare for pregnancy and the fertilised egg is expelled.

In India, the clinical trials started for AFV on humans before conducting all the animal tests much against the 1978 safety guidelines laid down by WHO for conducting research on anti-fertility vaccines. Serious concerns have been voiced about its possible impact on the spread of HIV and other infectious diseases. It is also well known that women are more prone to developing auto immune diseases. Yet researchers doing AFV research argue there is no scientific evidence to indicate whether AFV, per se, would increase or reduce the risk of HIV infection, except that it is a non-barrier method.

Given the reality that even an IUD can be inserted in women without their knowledge, there is every danger of a similar likelihood with AFV.

Either it be injectable contraceptives or the AFV or any other such drug, they should assure safety in breast feeding, long term safety for the women's reproductive system and most importantly should assure return to fertility. None of the contraceptives including IUDs and the oral pill seem to assure that. Neither are they sensitive to the social and cultural disruption that prolonged menstrual chaos and excessive bleeding can cause for women.

One should recollect that injectable contraceptives did not get US FDA approval for almost 20 years, mainly because of evidence, in the WHO's multi-centre trials, of a carcinogenic effect. An escape hatch was provided when the WHO changed its directives for contraceptive research and ruled that evidence from animal studies was not fully indicative of a contraceptive's side-effects. The trials, conducted mainly in the third world, subsequently concluded that injectables were relatively safe, but the details of the clinical trial's results were not made public.

It is important to reassert that the findings of all drug research especially if they are to be marketed in public must be available in the public domain. Answers to questions -- like who is doing the research, who is funding who, what are the research and treatment protocols, what are the short-term and long-term effects on women and her progeny, and what are the arrangements for monitoring adverse reactions and effects once they are introduced in the market -- must be the least that is available from the office of the Drug Controller of India; and nowadays they ought to be made available on the web also.

3.7 "Social Marketing" of Contraceptives

The term itself is deceptive and a misnomer. Social marketing is making the contraceptive available to NGOs and on prescription by private practitioners. There is concern that the contraceptive will not be available in the government health care system. Social marketing, which includes over-the-counter sales, inevitably leads to ill-informed use of the contraceptives without an understanding of the side-effects, or of the meaning of symptoms that may manifest upon use. Social marketing requires good backup and referral services so that the woman can consult in times of emergency and adverse symptoms. With the liberalization of the economy there has been a dramatic change also in the field of medical research. Social marketing of contraceptive drugs by NGOs and private practitioners supported by large grants from drug companies and international funding agencies is a cause for concern, since they (the so-called NGOs) are more or less only implementing agencies. There is a disturbing trend of doing some version of "Post Marketing Surveillance (PMS)" in place of Phase IV clinical trials by accepted methods of valid research and by accredited bodies.

Generally, animal and clinical trials of contraceptive drugs only test safety and efficacy in the short run and

the long-term and rare side-effects are not detected. A continued PMS over a long period of time is necessary to detect the long-term effects of these drugs. It is doubtful that clinical trials and PMS conducted by a pharmaceutical company would be objective, since it is driven by the profit motive rather than concern for public health, in this case, women's health. While no PMS on Net En has been made public since its approval for marketing, Pharmacia-Upjohn, manufacturers of Depo-Provera conducted a PMS for their product between June 1994 and December 1997 and the report was made public only in 2000. Though the manufacturers projected it as a five-year study, the PMS was conducted over three years. It studied each woman user for 15 months only, while the intended duration of Depo-Provera is 2 to 3 years. Therefore, 15 months is inadequate to assess long-term effects and cannot be declared as "safe" on the basis of inadequate data. The study does not assess the potential side- effect of loss of bone-density and risk of osteoporosis, the risk of cancer, no assessment of return of fertility has been made, neither has the effect on the progeny conceived accidentally or immediately on discontinuation of use of Depo-Provera has been studied. Problems such as amenorrhea, irregular bleeding, generalized weakness, migraine headaches and severe abdominal cramps were considered "non-serious" (Bal et al., 2001). In the case of Depo, on the other hand there is evidence to show it is life-threatening (see Satyamala, op.cit) and association with breast cancer has not been ruled out.

The entire burden of contraception and its side-effects no matter how serious is borne by women as also the outcome of conception whether it is an unsafe abortion or an unwanted pregnancy and/or the birth of an illegitimate child. The responsible sexual behaviour of the "inflictor" of pregnancy is never addressed as aggressively as are the women targeted for the contraceptives. It is little wonder that potentially hazardous contraceptives for women are preferred to safer cheaper, easier, male contraceptive methods including condom and non-scalpel vasectomy. "Social" marketing is a tool for abetting such unethical promotion. Abandoning PMS or diluting it only compounds the problem.

4. Hormonal Replacement Therapy (HRT)

HRT is a classic case of the industry exploiting the women's "market". The leading products under the label of HRT seek to promote estrogens for use by postmenopausal women. The attempt is to portray a natural process like menopause as a disease condition, which needs treatment. Menopause results in the cessation of production of estrogen and progesterone. HRT tries to fill this gap by ingesting these very hormones. Studies have shown that long-term use of unopposed estrogen can lead to increase in risk of endometrial cancer.[14] While HRT may be indicated for some women for problematic postmenopausal syndrome, its aggressive promotion for all post menopausal women is irrational and unethical.

The jury is still out on whether hormone therapy increases women's risk for recurrence of a new cancer, but most experts agree that the risks and unknowns outweigh the benefits at this point. In July 2002, the NIH (National Institutes of Health of USA) stopped a large study on Hormone Replacement Therapy early because of a significant increase in breast cancer risk for women taking a certain type of hormone replacement treatment. The study suggested that women who have been on combined HRT (estrogen plus a progestin) for more than 4 years should consult their doctors about whether they need to continue on HRT, and address their increased risks for breast cancer and heart disease for continued use of HRT. Also, it was suggested by the study that women taking HRT solely for heart disease prevention should stop taking HRT and consider other options.

While the study found that HRT does reduce the risk for fractures, researchers nevertheless suggest that women taking HRT to prevent osteoporosis should weigh the risks of HRT against the possible benefits with their doctors, and consider other, non-hormonal options for the treatment of osteoporosis.[15]

There is also deep concern at routine oophrectomies (surgical removal of ovaries) being done along with hysterectomies (surgical removal of uterus) in young women with bleeding problems. This results in sudden menopause (the so-called medical menopause) and subsequent creation of dependence on HRT.

5. Other Concerns

There are many areas where pharmaceutical companies are active in search for new drugs. All these need to be seen with due concern given the track record of many a drug company.

5.1 RU-486: the Abortion Pill

RU-486 (or Mifepristone) is a steroid hormone similar in structure to the natural hormone progesterone. Invented in 1980 by Dr. Etienne-Emile Baulieu for the French pharmaceutical company Roussel-Uclaf, RU-486 is the first of a new generation of birth control drugs called "antiprogestins", considered to be a breakthrough in birth control technology. (RU-486's name comes from Roussel-Uclaf's initials plus a serial number.)

In a woman's body, the natural hormone known as progesterone is essential for establishing and maintaining a pregnancy. The name for the hormone, in fact, comes from the Latin words "pro" (for) and "gestare" (to carry). RU-486 is a progesterone antagonist (an "antiprogestin"). Mifepristone or RU-486 antagonizes the effect of progesterone secreted by the body, which retains and sustains pregnancy. When administered to a pregnant woman, it stops the growth of fetus leading to its death.

Misoprostol, another drug, stimulates the effect of prostaglandin, which causes contraction of the uterus, when administered after mifepristone, the uterus undergoes powerful contraction and expels the already dead foetus. Although "Misoprostol" is approved for abdominal ulcers, the literature specifically contains a warning that this drug should not be taken by pregnant woman, as it may induce abortion, the manufacturers are advertising it in a negative way that this drug can be used for abortions.

About one percent of women who take the drug combination experience heavy bleeding which requires further treatment. In clinical studies on RU-486, incomplete abortion occurred in 2-3% of cases and pregnancy persisted in 1%. These women then required surgical abortions.

Dr S G Kabra in a petition before the Rajasthan State Human Rights Commission raised an objection that mifepristone (or RU-486), used for bringing about MTP is being sold freely across the counter, therefore, being misused and abused resulting sometimes in the death of pregnant women on account of excessive bleeding. It was also contended by him that this drug could be sold only on the prescription of a registered gynaecologist for use either in the hospital or at the recognised centres, where necessary facilities for bringing about the termination of pregnancy are available, including the facility for blood transfusion.

He further contended that on account of free sale of the drug across the counter, anybody could purchase it and give it to pregnant women, especially in the rural areas, where many women have been found to die on account of excessive bleeding or other complications. He also stated in his petition that The Medical Termination of Pregnancy Act, 1971 permits termination of pregnancy up to 20 weeks of gestation for stipulated conditions, of approved centres, by approved doctors and after stipulated certification by physicians under strict compliance, monitoring and surveillance of the Medical Termination of Pregnancy Rules, 1975 and the Medical Termination of Pregnancy Regulations, 1975.

The reported data in the official publication, *Year Book of Family Welfare in India,* reveals that there are over four lakh registered abortions done in the country every year of which approximately 40,000 are in Rajasthan. Illegal abortions far exceed than the reported number. The proportion of legal to illegal is 1: 8. A very high percentage of these illegally done abortions develop severe complications and are attended with high morbidity and mortality, when a woman develops life-threatening complications.

The Drugs Controller General India has approved mifepristone as abortifacient to be manufactured, marketed and sold with mandatory stipulations under the various provisions of Drugs and Cosmetics Act. Mifepristone is approved to be made available for Medical Termination of Pregnancy (MTP) strictly under the provisions of Medical Termination of Pregnancy Act, 1971 (MTP Act), under the MTP Act, pregnancy can be terminated (1) by approved Physicians (2) at approved Centres (3) for approved indications and (4) for approved duration. The MTP Rules and MTP Regulations govern each of these four stipulations.

As per the above mentioned legal provisions, the doctors approved under the MTP Act alone can do MTP. All qualified Physicians registered under the MCI Act cannot do it. Only those meeting the stipulated approval under the MTP Act can do it. It is only those approved doctors and centers that can under the law, prescribe and administer mifepristone. The commission further held that the pharmaceutical companies are to market the drugs in conformity of the MTP Act for which it has been specifically approved.

"Those who make available mifepristone or misoprostol to be administered in contravention of the provisions of the Drugs and Cosmetics Act and the MTP Act along with those who prescribe and administer it in contravention of the Acts are liable to be prosecuted under the provisions of the Indian Penal Code in addition to the provisions of the two Acts." This decision was given by the Commission on March 20, 2004 in Petition no. 03/17/260 by Dr S G Kabra to curb the free sale of mifepristone/misoprostol formulations. The commission sent its recommendations to State Drugs Controller, Rajasthan, on March 27, 2004 and the Drugs Controller, Rajasthan sent copies of the Order to M/S Cipla Ltd, Jaipur; M/s Sun Pharmaceuticals Ind. Ltd, Jaipur; M/s Cadila Health Care Ltd(Zydus Alidac), Jaipur; all State ADC's and DCO's for compliance with the directives on April 1, 2004.

In India, the so-called illegal abortion (that is done by persons who are not registered doctors) is common and the reality is that most drugs are available over the counter. Taking RU-486 and its variants is a bit risky even with medical supervision and is certainly more risky without emergency ambulatory services in case of heavy bleeding, etc.

5.2 India as a "Destination" for Clinical Trials

India is becoming a favoured destination for clinical trials. (We have discussed this issue elsewhere in the book in more detail.)

The reasons for such "popularity" seems to be: (a) Large population and genetic diversity (b) Low cost (c) Legislative vacuum or infirmities (d) Ignorance about the legal and ethical issues of human trials among the public and even among health care professionals and (e) Craze among the developing countries to link up with Western institutions unthinkingly and at any cost.[16] The fee for import of a new bulk drug or formulation is fixed at Rs 50,000, whereas the fee for import of a new fixed dose combination is fixed at Rs 15,000.The application fee for phase I clinical trials will be Rs 50,000 and the fee for both phase II and phase III trials, it is just Rs 25,000 each. Many of these companies will of course get "informed consent" of illiterate poor people and probably women will be targeted with drugs known and unknown.[17]

Who is doing what trials need to be placed in the public domain. It is important to ensure that vulnerable segments of the population like poor, especially poor women and children are not exploited merely for money in the process of a clinical trial. Companies need to have commitment to adequate short-term emergency and long-term follow-up on adverse effects of drugs.

5.3 Human Cloning and Embryo Research

The whole area of human cloning is fraught with possibilities of violation of human rights in general and in particular, rights of women's health and reproductive rights. Human cloning for it's further advancement will require among other things mass experimentation on women and children. Cloning advocates, in as much as drug companies pushing contraceptives, tend to appropriate the language of reproductive rights and freedom of choice to support their case. This is absurd and needs to be countered forcefully. "There is an immense difference between ending an unwanted pregnancy and creating a duplicate human. Most people readily understand this, and can support abortion rights while opposing human cloning…. We also call for a moratorium of five years on the use of cloning to create human embryos for research purposes. At the same time we support research that would help to determine whether stem cells have therapeutic effects. Adult stem cells, umbilical cord stem cells, and embryonic stem cells that have not been derived from embryos created for research can be used for these purposes. The creation of clonal human embryos, which would increase the difficulty of enforcing a ban on the production of genetic duplicate humans, is unnecessary for these investigations. This moratorium is prudent and reasonable policy when faced with a technology of such profound consequence…. More than thirty countries worldwide have already banned the creation of human clones and/or imposed constraints on the creation of clonal human embryos…. The future of our common humanity is at stake."[18]

Of late, a subject of emerging concern has been the proliferating area of Assisted Reproductive Technologies wherein for procedures like intrauterine insemination or in vitro fertilization (IVF), ovulation drugs are used to correct various hormonal imbalances and stimulate ovulation with a view to create favourable conditions, for say, an embryo implant. The most commonly prescribed ovulation drugs are clomiphene citrate, follicle stimulating hormone (FSH), human chorionic gonadotropin (hCG), and human menopausal gonadotropin (hMG). These and four others, bromocriptine, cabergoline, gonadotropin releasing hormone (GnRH), and GnRH analogs, which have very specialized applications. Many of these drugs (see Table below for other effects) are also possibly carcinogenic.[19] In another study, it was concluded: "Long-term use of certain infertility drugs could adversely affect risk of breast cancer. Additional confirmatory studies are needed."[20]

Ovulation Drugs, their Forms and Most Common Side-Effects[21]		
Generic Name	**Form**	**Most Common Side-Effects**
Clomiphene citrate	Tablets	• Increased incidence of multiple births, • miscarriage • thick, dry cervical mucus • hot flashes, nausea, breast tenderness • occasional headaches or blurred vision • depression, mood swings • ovarian cysts, pelvic discomfort
Follicle Stimulating Hormone (FSH) Injection	Injection	• increased incidence of multiple births • increased incidence of miscarriage and premature delivery • breast tenderness, swelling, or rash at injection site • mood swings, depression • mild to severe hyperstimulation syndrome (enlarged ovaries, abdominal pain, and bloating)
Human Chorionic Gonadotropin (hCG)	Injection	No known side-effects if only taking hCG
Human Menopausal Gonadotropin (hMG)	Injection	Same as for FSH
Bromocriptine Cabergoline	Capsules/Tablets	Nausea, vomiting, nasal congestion headache, dizziness, fainting decreased blood pressure
Gonadotropin-Releasing Hormone (GnRH)	Injection	• Slight chance of multiple births, mild hyperstimulation syndrome • headache • nausea
GnRH Analogs Injection	Injection (Leuprolide Acetate) Nasal Spray (Nafarelin Acetate) Injection (Goserelin Acetate)	• Hot flashes, headache • mood swings, insomnia • vaginal dryness • decreased breast size • painful intercourse • bone loss • severe joint pain • chest pain • nausea • dimness of vision • loss of pituitary function • hypertension • rapid heart beats • asthma • generalized oedema • abnormal liver function
GnRH Antagonists	Injection (Ganirelix Acetate)	• Same as GnRH Analogs

Many of these drugs used to "hyperstimulate" the ovaries also have other negative effects, most notably a condition called Ovarian Hyperstimulation Syndrome (OHSS).

According to Suzanne Parisian, a former Chief Medical Officer of the US FDA:[22]

> …The long term health risks for a woman receiving IVF drugs for egg retrieval are unknown…
>
> … Regarding potential acute short-term risks which have been seen in stimulation trials submitted to FDA, severe Ovarian Hyper-Stimulation Syndrome (OHSS) occurs rarely - in about 3-8% of patients. This condition that results from over-stimulation of the ovary can progress rapidly to a serious life-threatening condition days after completion of egg collection. Based on symptoms, it is classified as mild (7%) or moderate to severe (1%). OHSS has been associated with death and has been reported in women with polycystic ovaries, in younger women, and in women with high estrogen hormone levels and after a woman receives either GnRH agonist or hCG. OHSS carries an increased risk of clotting disorders, kidney damage, and ovarian twisting. Ovarian stimulation in general has been associated with serious life threatening pulmonary conditions in FDA trials including thromboembolic events, pulmonary embolism, pulmonary infarction, cerebral vascular accident (stroke) and arterial occlusion with loss of a limb and death.
>
> Risks of the egg retrieval procedure, although rare, include death, respiratory or cardiac arrest, brain damage, paraplegia, paralysis, loss of function of a limb or organ, hemorrhage, allergic reaction, and infection. Bleeding or other injuries which occur during retrieval may require an invasive surgical procedure to correct and could affect future fertility…
>
> … All stimulation drugs are Pregnancy X - which means they are contraindicated for use in women that are pregnant due to a lack of information regarding the safety of these drugs during pregnancy
>
> … there is an unfortunate and false assumption of the public, legislators, press and physicians that all current IVF stimulation drugs have been scientifically recognized as "safe" by the FDA and suitable for use in healthy women for multiple egg extraction. That simply and sadly is not correct.

The assault on women's bodies seems to be from multiple sources. On the one hand over-medicalization of women's bodies has led to the use and purchase of expensive drugs and equipments rather than addressing major health problems like anaemia, safe abortion, safe delivery, etc. On the other, the pharmaceutical industry, the biotech industry and the baby-infertility business combined with health tourism industry has given rise to new concerns.

The task for the Drugs Controller General of India and the Ministry of Health and Family Welfare is cut out. Whether they will rise to the challenge is to be seen.

Poster of the The Canadian Women's Health Network at <http://www.cwhn.ca/resources/cwhn/swallow.html>, Copyright © 2006, Posted: March 8, 2006

References

Bal, Vineeta; Murthy, Laxmi; Subramanian, Vani: Population growth and coercive controls : case of injectable contraceptives. Economic and Political Weekly. 34(39). Sept. 25-Oct 1, 1999. p.2776-2778.

Bal, Vineeta, Laxmi Murthy, and Vani Subramanian."Net En: Reflections on the History of the struggle Against Injectable Contraceptives", *Medico Friend Circle Bulletin,* January-February 2001, Mumbai

Balasubrahmanian, Vimal:: Fix it, Forget it: Norplant and Human Rights. Economic and Political Weekly. Vol. 28(22). May 29, 1993. P.1088.

Chowdhury Zafrullah. *The Politics of Essential Drugs: making of a successful health strategy. Lessons from Bangladesh*. Vistaar Publications, N.Delhi, 1995.

Chowdhury Ranjit Roy (1999). "Rational use of Drugs, Delhi's change of policy, changes lives", *Essential Drug Monitor* (No. 27, DAP, WHO, Geneva).

Correa C.M. (1997). *The Uruguay Round and Drugs*. WHO Task Force on Health and Economics/Action Programme on Essential drugs, Geneva, 1996.

Gopalan, Sarala and Mira Shiva (eds). *National Profile on Women, Health and Development, Country Profile - India*. Voluntary Health Association of India and WHO, New Delhi, 2000.

Report of the Hathi Committee, Government of India, 1975.

LOCOST. *A Lay Person's Guide to Medicine What is behind them and how to use them*. Low Cost Standard Therapeutics (LOCOST), Baroda, December 2000. This present book is the updated version.

National Working Group on Patent Laws, N.Delhi, various publications 1989-2002

Phadke, Anant. *Drug Supply and Use Towards Rational Policy in India*. Sage

Publications, N.Delhi, 1998.

PIL No. 698/1993 filed in Supreme Court by DAFK/ AIDAN

Saheli. 'Enough is Enough: Injectable Contraceptive Net En- A Chronicle of Health Hazards Foretold'. 1998, N.Delhi

Sathyamala, C. *An Epidemiological Review of the Injectable Contraceptive, Depo-Provera* . Medico Friend Circle and Forum for Women's Health, Pune, 2000.

Shiva, Mira and Rane, W.V. *Rational Selection of Drugs*. VHAI and AIDAN, N.Delhi, 1986

Shiva, Mira and Rane W.V. *Banned and Bannable Drug List*. VHAI. N.Delhi, Revised edition 2004.

Unnikrishnan P.V. and Shiva Mira. *Sura Tragedy*. VHAI, N.Delhi, 1992

UN Centre on Transnational Corporations. *Consolidated list of products whose consumption and/or sale has been banned withdrawn, or severely restricted or not approved by Governments*. New York, 1986.

WHO Technical Report Series (TRS) on Essential Drug Selection and Lists: TRS Nos. 615, 641, 722, 770, 796, 825, 850, 867 (1977, 1979, 1983, 1985, 1988, 1992, 1995, 1997). And the latest list of 2005.

UNDP (1999). *Human Development Report*.

RFSTE. *The Biopiracy Factsheets*. Research Foundation for Science Technology and Ecology, Dehradun, 1998.

Shiva Vandana. *Biopiracy*. Research Foundation for Science Technology and Ecology , Dehradun, 1997.

Endnotes

[1] The National Family Health Survey 1998-99 shows the only 52 percent of the women were involved in decisions about their own health. Out of the 39 percent who had experienced a reproductive health problem like abnormal vaginal discharge, symptoms of urinary tract infection, pain or bleeding during intercourse, 66 percent did not seek any advice or treatment.

[2] "GAO Study on women in clinical trials", quoted in "Women and Drugs" section of Chetley, A. *Problem Drugs*, Amsterdam, HAI, 1993.
See also: "Drug Therapy and Gender" Viviana Simon, PhD, Eileen Resnick, PhD, Society for Women's Health Research, Washington, DC, <http://www.uspharmacist.com/index.asp?show=article&page=8_1333.htm>

[4] Chetley, op.cit.

[5] Source: "Does Sex Make a Difference?" at < http://www.fda.gov/fdac/features/2005/405_sex.html>

[6] For more information see Chetley, op.cit.

[7] Laurence, D.R and Bennett, P.N. *Clinical Pharmacology*. London, Churchill Livingstone, 6th Edn., 1987, p.85, quoted in Chetley, op.cit.

[8] See for instance: Trent Stephens and Rock Brynner. *Dark Remedy: The impact of thalidomide and its revival as a vital medicine.* Perseus Books Group, Jan 2001. See also the USFDA site at <http://www.fda.gov/cder/foi/label/2001/20785s12s14lbl.pdf>

[9] For references see, Centers for Disease Control and Prevention, <http://www.cdc.gov/DES/hcp/bibliography/index.html>

[10] See also: Shree Mulay. "Quinacrine non-surgical sterilisation: troubling questions", at <http://www.issuesinmedicalethics.org/083or087.html>; and Mohan Rao, "Quinacrine Sterilisation Trials: A Scientific Scandal?" *Economic and Political Weekly,* March 28, 1998.

[11] Sathyamala, C. *An Epidemiological Review of the Injectable Contraceptive, Depo-Provera.* MFC and Forum for Women's Health, Pune, 2000). This book is compulsory reading for anybody concerned about the issue.

[12] "Black Box Warning Added Concerning Long-Term Use of Depo-Provera Contraceptive Injection" at <http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01325.html>, November 17, 2004

[13] See for instance, Mintzes, Barbnara et al. *Norplant: Under her Skin.* Women's Health Action Foundation and WEMOS, Delft, 1993.

[14] See HRT related information at Medline: <http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a601041.html>. The NIH press release, "NHLBI Stops Trial of Estrogen Plus Progestin Due to Increased Breast Cancer Risk, Lack of Overall Benefit" at <http://www.nhlbi.nih.gov/new/press/02-07-09.htm.> "Why did the NIH stop the trial? Your questions answered" at <http://www.nhlbi.nih.gov/whi/e-a_faq.htm>

[15] See also: for a review of various recently cited studies: <http://bmj.bmjjournals.com/cgi/collection/menopause>, <http://www.breastcancer.org/qanda_menopause.html#progesterone> and "HRT in the News, The Women's Health Initiative Study at a Glance." <http://www.cwhn.ca/resources/menopause/hrt-glance.html>

[16] *Frontline*, Aug. 18 - 31, 2001, Interview with Dr Valiathan, "Clinical trials should promote health care."

[17] See *Frontline*, op.cit., Drug Trials and Ethics. See also discussion in Chapter 5 of this book.

[18] Statement on Cloning, Boston Women's Health Collective, June 2001

[19] See for instance: Ali Mahdavi, M.D.,a Tanja Pejovic, M.D., and Farr Nezhat, M.D. "Induction of ovulation and ovarian cancer: a critical review of the literature". *Fertility and Sterility*, Vol. 85, No. 4, April 2006. The study concludes: "Despite the overall reassuring findings of the available studies, there is a need for well-designed clinical trials to understand the possible carcinogenic effects of the ovulation-inducing drugs."

[20] Ronald T. Burkman, M.D., et al. "Infertility drugs and the risk of breast cancer: findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study." *Fertility and Sterility*, Vol. 79, No. 4, April 2003.

[21] Source: American Society for Reproductive Medicine. *Ovulation Drugs: A Guide for Patients.* 2000.

[22] Open Letter from Suzanne Parisian, Feb 2005. See <http: //www.genetics-and-society.org/resources/items/200502_letter_parisian.html.> See also: Judy Norsigian. "Egg Donation For IVF And Stem Cell Research: Time to Weigh the Risks to Women's Health." *Differntakes* No. 33 ~ Spring 2005.

Chapter 9

What is to be done?

Thirty years ago, medicines policy was a technical discourse mainly among UN agencies, ministries of health, and international experts. However, the growing AIDS pandemic has galvanized discussions about access to treatment. The United Nations, donors, recipient governments, and suppliers are being pressured by a growing global network of public interest NGOs and civil society groups that need medicines and are not able to get them. New bodies, such as the GFATM, have been founded to provide financing for national programs to tackle three of the major diseases of poverty. Existing organizations, both public and private, have become increasingly engaged in finding new ways to increase access to medicines. But more needs to be done, and it will require new thinking and new approaches.

In the last decade, most developing countries have undertaken measures to improve access to medicines, with varying degrees of success. Even where there have been setbacks, the experience gained strongly indicates that progress is possible. Where both the initiatives and the results have been monitored, lessons emerge that can be adapted to local conditions and applied elsewhere. A key finding is the need to involve the community in developing health system policies and programming.

- UN Millennium Project. 2005. *Prescription for Healthy Development: Increasing Access to Medicines*[1]

There are 2 analogies I want to leave you with to illustrate the unreasonableness of CDER's standard of evidence as applied to safety, both pre- and post-approval. If the weather-man says there is an 80% chance of rain, most people would bring an umbrella. Using CDER's standard, you wouldn't bring an umbrella until there was a 95% or greater chance of rain. The second analogy is more graphic, but I think it brings home the point more clearly. Imagine for a moment that you have a pistol with a barrel having 100 chambers. Now, randomly place 95 bullets into those chambers. The gun represents a drug and the bullets represent a serious safety problem. Using CDER's standard, only when you have 95 bullets or more in the gun will you agree that the gun is loaded and a safety problem exists. Let's remove 5 bullets at random. We now have 90 bullets distributed across 100 chambers. Because there is only a 90% chance that a bullet will fire when I pull the trigger, CDER would conclude that the gun is not loaded and that the drug is safe.

- Dr David J. Graham, MD, MPH, testimony before US Senate Committee, November 18, 2004

In this book we have surveyed, within the limits of space, factors that have and will impinge on drug availability in India. The situation is quite dismal in terms of availability of medicines for the poor and in terms of access to health care, and there are enormous concerns of safety and rationality of the drugs available in India.

In the coming years, issues of access to drugs, highlighted by lack of access to drugs for TB, malaria, HIV/AIDS and a host of communicable and non-communicable diseases, are likely to gain prominence. Closely related issues are regulation of drug pricing and drug patent issues on newly emerging drugs for diseases of

public health importance. An area of concern would be the mindless enlargement of a vaccine-for-every-disease policy rather than looking at the root causes of ill-health: typified by "let us have diarrhoea vaccine if we cannot provide clean drinking water". Therapeutic and populist fashions seem to dictate health policies than evidence-based risk/benefit analysis.[2]

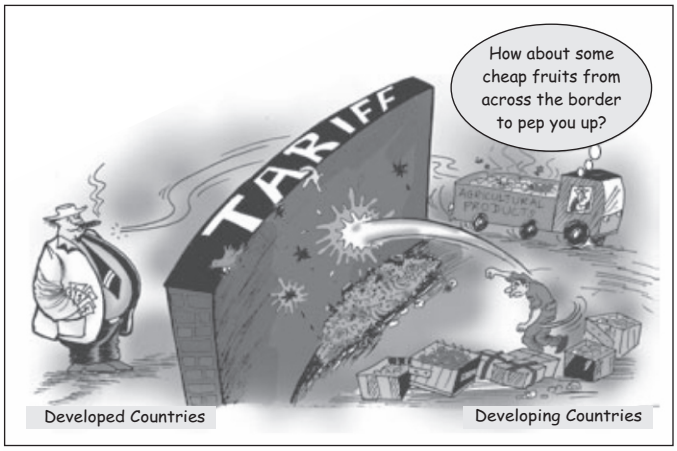
The other worry is the lack of safeguards in clinical trials even as India becomes a destination for contract research and clinical trial outsourcing.

Indeed a situation of poverty and chaos amidst booming pharma scrips and international hosannas.

What then needs to be done? A minimum wish list would include:[3]

- Recognise access to medicines and health as a human rights issue.
- Incorporate explicitly gender concerns in pharma policy making and marketing of drugs.[4]
- Restricting drugs available in India to essential drugs as per the Government's own NLEM (2003) or the 14th Model List of Essential Medicines (March 2005) of the WHO.[5]
- A comprehensive Rational Drug Policy that includes no unnecessary formulation presentations in terms of syrups, capsules and injections; a vaccine policy strictly guided by science of public health and prioritization of use of public money; a limited list of over-the-counter drugs to be available.
- Promotion of drugs under only generic names with strict regulation of promotional activities of drug companies; strict guidelines of sponsorship, if at all, of medical symposia and other scientific meetings.
- Mandatory disclosure of funding and potential conflicts of interests in all clinical trials, medical research and publications as also by policy makers and members in various government committees related to pharmaceuticals and health.
- A limit on cross-practice; compulsory continuing medical education of doctors; improvement in medical education as well as medical education fee regulation; a systematic policy of research on non-allopathic drugs as well as a pricing and marketing policy for non-allopathic drugs.
- Weeding out all irrational and harmful medicines.
- Price Control on all essential drugs marketed in India.
- Introduction of Essential Drug Lists and Standard Treatment Guidelines, especially in health facilities of the governments at the Centre and State followed by legal changes to enable production and marketing of only essential drugs in India (that is in both private and public sectors).

- Access to objective information on drug risks and hazards from the Drug Controller General of India.
- Transparent Pooled procurement in all States as in Tamil Nadu and Delhi State Governments after assessing rational, essential drug needs (which has resulted in procurement of drugs for the public health facilities at a rate which is up to 2% of the prices in the retail market!).
- Implementing the Mashelkar Committee recommendations without centralization and bureaucratization.
- Action on corruption at all levels of drug administration including in the drug industry.
- No product patents on diseases of the national programme and more careful orchestration of the health needs of India.
- Increasing the ease of getting/issuing compulsory licensing of drugs of importance to the people of India.
- Transparent decision making in matters of patents, pre-grant opposition, royalty, data exclusivity, etc., keeping in mind the interests of the people of India.
- Transparent access to information on clinical trials with a clinical registry accessible in the public domain.
- Specific research on gender-related aspects of medicines access and use by women and girls, and men and boys.


How about some cheap fruits from across the border to pep you up?
TARIFF
AGRICULTURAL PRODUCTS
Developed Countries
Developing Countries

Trading up, July-Sep 2005

- Universal Health Access and Health Insurance for every citizen of India by increasing the government's per capita expenditure on health and recognising user fees as a deterrent to access to health and medicines.[6]

The need for consumer action cannot be over-emphasised in view of the aggressive and unethical marketing practices employed by the pharmaceutical companies. Consumer awareness is an important pre-requisite for consumer action. Consumers, individually or as a group, can play a key role in protecting themselves and preventing unethical promotion of drugs, and unnecessary suffering caused by dangerous drugs or by irrational use of drugs.

Prescribers in turn can facilitate patient compliance of drugs by doing several things. For an illustrative list, see the box below.

Individual consumer action may be taken by:

✧Having basic knowledge of medicines and how they work.

✧Knowing which drugs are hazardous, banned or need to be avoided.

- ✧ Avoiding taking drugs that are useless and/or irrational.
- ✧ Asking your doctor to prescribe drugs by their generic names and avoiding OTC drugs whenever possible.
- ✧ Asking your doctor for more information on the drug you have been prescribed.
- ✧ Avoiding tonics and other health restoratives; instead ensuring a balanced diet for the whole family.
- ✧ Participating in activities of local consumer groups and drug action networks.
- ✧ Critically evaluating advertisements for health products.
- ✧ Reporting any unethical promotion of drugs to the local health or consumer group.

Aids to Improving Patient Adherence to Treatment

Patientleaflets
Patient leaflets reinforce the information given by the prescriber and pharmacist. The text should be in clear, common language and in easily legible print.

If the patient cannot read, try pictorials. If they are not available, make pictorials or short descriptions for your own P-drugs, and photocopy them.

Daycalendar
A day calendar indicates which drug should be taken at different times of the day. It can use words or pictorials: a low sun on the left for morning, a high sun for midday, a sinking sun for the end of the day and a moon for the night.

Drugpassport
A small book or leaflet with an overview of the different drugs that the patient is using, including recommended dosages.

Dosagebox
The dosage box is becoming popular in industrialised countries. It is especially helpful when many different drugs are used at different times during the day. The box has compartments for the different times per day (usually four), spread over seven days. It can then be refilled each week. If cost is a problem, the box can be made locally from cardboard. In tropical countries a cool and clean place to store the box will be necessary.

Even if the patient aids described here do not exist in your country, with creativity you can often find your own solutions. The important thing is to give your patients the information and tools they need to use drugs appropriately.

Source: *Guide to Good Prescribing. WHO Action Programme on Essential Drugs*, Geneva, 1995.

Group consumer action is more effective in bringing about necessary changes. It would require getting together like-minded people who are genuinely concerned about these issues. Groups may be formal or informal. Informal groups may be formed where people simply come together on single issues requiring urgent steps for redressal. Formal groups may be formed with a proper structure as per the rules of a society or a public trust.

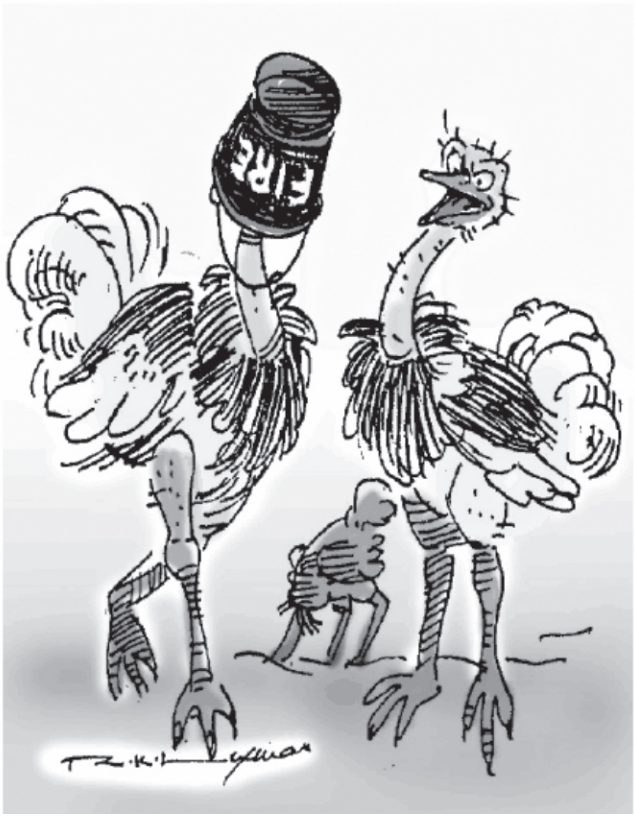
Some of the activities groups can undertake are:

✧create awareness of health issues and disseminate information.

✧bring out regular publications to keep consumers aware.

- organise and encourage people to participate in health activities.
- identify publications essential for drug information.
- ensure availability of preventive health amenities and services such as clean water, sanitation, immunisation and healthy environment in your neighbourhood, and safe working conditions at work place.
- report all drug shortages to the Drug Controller of India.
- participate in health and consumer campaigns.
- write in local press and publicise issues of concern.

Some all-India networks/groups/resource persons that can be consulted by consumer groups are the All-India Drug Action Network (AIDAN); Bulletin of Drug & Health Information (*BODHI*) (email: <bodhi_fha@dataone.in>; the Medico Friend Circle <www.mfcindia.org>; the Jan Swasthya Abhiyan (JSA) <http://phm-india.org>; Affordable Medicines & Treatment Campaign <http://www.lawyerscollective.org/lc_hivaids/amtc>; and *Indian Journal of Medical Ethics* <http://www.issuesinmedicalethics.org>; LOCOST, the publishers of this book <www.locostindia.org>.



R.K. Laxman in *Times of India*

Our traditional way of hiding is too old-fashioned for you, I suppose!

Endnotes

[1] *Report of the Task Force on HIV/AIDS, Malaria, TB, and Access to Essential Medicines, Working Group on Access to Essential Medicines.* Sterling, Va.: Earthcscan.

[2] The Hepatitis-B vaccine and related scare-mongering is an example. See "Why we do not need to give Hepatitis B vaccine for all newborns: Letter to Health Minister," *mfc bulletin,* 313-314, Oct 05 -Jan 06. See pp. 502-503 of this book.

[3] Some of the formulations are after Phadke, Anant. *Drug Supply and Use: Towards a Rational Drug Policy in India.* New Delhi: Sage Publications, 1998.

[4] The UN Millennium Project, 2005, report *Prescription for Healthy Development: Increasing Access to Medicines.* (Report of the Task Force on HIV/AIDS, Malaria, TB, and Access to Essential Medicines, Working Group on Access to Essential Medicines. Sterling, Va.: Earthcscan.) has this to say in its recommendations related to gender:

Nationally:

- Ensure women have access to accurate, gender-sensitive medicines information.
- Involve women in medicines policymaking.
- Promote innovative and outcome-based research in the gendered aspects of medicines access and use by women and girls and men and boys.
- Collect sex- and gender-disaggregated data on access and use, which, in combination with adequate gender analysis, should inform policies, plans, and budgets.
- Ensure that women and girls have equal access to medicines.
- Ensure full and equitable access to sexual and reproductive health services and commodities.
- Ensure that national essential medicines lists contain the core medicines and devices for sexual and reproductive health recommended by the UNFPA and WHO.

And internationally,

- organise and encourage people to participate in health activities
- identify publications essential for drug information
- ensure availability of preventive health amenities and services such as clean water, sanitation, immunisation and healthy environment in your neighbourhood, and safe working conditions at work place.

[5] For the 14th WHO Model List of Essential Medicines (2005), see <http://www.who.int/>. For National Essential Medicines List (NEML) 2003 see <http://www.expresspharmapulse.com/nedl.pdf >

[6] "…It may be asked, whether India has the resources today to give health care insurance to everybody. The answer is yes. We are already spending about 6% of our Gross Domestic Product (GDP) on health-care. But the state's share in only 21% of this expenditure. This share is lower than that seen even in Bangladesh (33%) and Pakistan (53%). In most developed capitalist countries, this share is 70 to 80% and even in the U.S. - the supposed heaven of private medical care, the state's share in total health-expenditure is 44%. … the governments in Sri Lanka, Bangladesh, Pakistan … spend a higher proportion for health-care than private health-expenditure, why can't the Indian government do this? The people are already paying 4.5% of GDP in the private sector. If the government spends 5% of GDP on health-care by almost quadruplicating its current health-expenses, then an additional special health-tax proportional to income, to meet the extra needs for a Universal Health Insurance can be justified. Instead of paying directly to the often exploitative private sector as is done today, people would be willing to pay a health-tax to the local government who could in turn pay

the private practitioners as per negotiated, rational rate-structure. Thus without people having to pay more on health-care than what they are paying today, India can provide for expenses for a Universal Health Insurance of up to 9.5% of GDP. This much expense should suffice. Though higher in absolute terms, the health-expenditure in Japan, Germany, Canada, France is in the range of 4.5 to 9.5% of the GDP. What is needed in India is intensive public pressure on the Indian government to divert more resources towards health-care." (Phadke 1998, op.cit., chapter on "What Can be Done?")

Laws pertaining to Drug Production and Use in India

In the beginning of the current (20^{th}) century, Drug Industry was practically non-existent in India and pharmaceuticals were being important from abroad. The first world war changed the situation and not only were finished and cheap drugs imported in increasing volume, the demand for indigenous products also were voiced from all sides. With the clamour for swadeshi goods manufacturing concerns, both Indian and Foreign, sprang up to produce pharmaceuticals at cheaper rates to compete with imported products. Naturally some of these were of inferior quality and harmful for public health. The Government was, therefore, called upon to take notice of the situation and consider the matter of introducing legislation to control the manufacture, distribution and sale of drugs and medicines.

Two of the laws, The Poisons Act and the Dangerous Drugs Act were passed in 1919 and 1930 respectively. The Opium Act was quite old having being adopted as early as 1878. But to have a comprehensive legislation, which the rapid expansion of the pharmaceutical production and drug market required by the end of the second decade for its control, the Indian Government appointed, in 1931, a Drugs Enquiry Committee under the Chairmanship Lt. Col. R. N. Chopra which was asked to make sifting enquiries into the whole matter of drug production, distribution and sale by inviting opinions and meeting concerned people. The Committee was asked to make recommendations about the ways and means of controlling the production and sale of drugs and pharmaceuticals in the interest of public health. The Chopra Committee toured all over the country and after carefully examining the data placed before it, submitted a voluminous report to government suggesting creation of drug control machinery at the centre with branches in all provinces. For an efficient and speedy working of the controlling department the committee also recommended the establishment of a well-equipped Central Drugs Laboratory with competent staff and experts in various branches for data standardization work. Under the guidance of the Central Laboratory, it was suggested, small laboratories would work, in the provinces. For the training of young men and women, the Committee recommended the permission of Central Pharmacy Council, and the Provincial Pharmacy Councils, with registrars who would maintain the lists containing names and addresses of the licensed pharmacists.

The outbreak of the second world war in 1939 delayed the introduction of legislation on the lines suggested by the Chopra Committee which the Indian government contemplated and considered as urgent. However, the Drugs Act was passed in 1940 partly implementing the Chopra recommendations. With the achievement of independence in 1947 the rest of the required laws were put on the Statute Book. In 1985, the Narcotic Drugs and Psychotropic Substances Act was enacted repealing the Dangerous Drugs Act 1930 and the Opium Act of 1878.

At present the following Acts and Rules made thereunder that govern the manufacture, sale, import, export and clinical research of drugs and cosmetics in India.

The Drugs and Cosmetics Act, 1940

The Pharmacy Act, 1948

The Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954

The Narcotic Drugs and Psychotropic Substances Act, 1985

The Medicinal and Toilet Preparations (Excise Duties) Act, 1956

The Drugs (Prices Control) Order 1995 (under the Essential Commodities Act)

Some Other Laws

There are some other laws which have a bearing on pharmaceutical manufacture, distribution and sale in India. The important ones being:

1. The Industries (Development and Regulation) Act, 1951
2. The Trade and Merchandise Marks Act, 1958
3. The Indian Patent and Design Act, 1970
4. Factories Act

Source: Central Drugs Standard Control Organization at <http://www.cdsco.nic.in/index.html>

March 24, 2006
April 7, 2006

Pharmaceutical Website Links

A few of these links are repetitive and overlapping.

Government of India

1) Central Drugs Standard Control Organisation, <http://cdsco.nic.in/>

2) Ministry of Health and Family Welfare, <http://www.mohfw.nic.in/>

3) National Pharmaceuticals Policy, 2006; Recommendations of the Task Force constituted under the Chairmanship of Dr. Pronab Sen to explore issues other than price control to make available life-saving drugs at reasonable prices, <http://chemicals.nic.in/>

4) Report of the National Commission on Macroeconomics and Health, <http://mohfw.nic.in/reports_on_ncmh.htm>

5) Pharmaceutical Policy 2002 and previous drug price control policies at,

<http://www.nppaindia.nic.in>

6) National Essential Medicines List (NEML) 2003, <http://www.expresspharmapulse.com/nedl.pdf>

7) National Health Policy (NHP),

<http://mohfw.nic.in/np2002.htm>

8) National Family and Health Survey,

<http://www.nfhsindia.org/>

9) Approved L1 rates for the supply of Drugs of the Tamil Nadu Medical Services Corporation, <http://www.tnmsc.com/>

10) National AIDS Control Organization,

<http://www.naco.nic.in/>

11) Indian Council of Medical Research,

<http://www.icmr.nic.in/>

12) Food and Drug Control Administration (FDCA), Gujarat,

<http://www.gujhealth.gov.in/FDCA>

13) “One point resource of peer reviewed Indian biomedical literature covering full text of IndMED journals including the, Indian Journal of Pharmacology, <http://medind.nic.in/ibi/ibim.shtml> <http://medind.nic.in/>

Pharma and Health related NGOs/Organisations

14) LOCOST, the publishers of this book, <www.locostindia.org>

15) Medico Friend Circle, <www.mfcindia.org>

Affordable Medicines & Treatment Campaign,
<http://www.lawyerscollective.org/lc_hivaids/amtc>

16) *Indian Journal of Medical Ethics,* < http://www.issuesinmedicalethics.org>

17) People’s Health Movement and Links,
<http://phmovement.org/links/index.html>

18) Jan Swasthya Abhiyan (JSA), <http://phm-india.org>

19) Center for Enquiry Into Health and Allied Themes (CEHAT),
<http://www.cehat.org/ >

20) Action North East Trust, Assam, India.
Active in Rational Drug Therapy advocacy especially in the North East of India. See their malaria booklet at the site,
<http://www.theant.org/>

21) Bharat Vaidika Sanastha focusing on Primary Health Care, see also the related links,
<http://www.bharatvaidyaka.org.in>

22) Jan Swasthya Sahyog (JSS), Bilaspur,
<http://www.geocities.com/jss_ganiyari/HOME.htm>

23) SAHAJ (Society for Health Alternatives), <www.sahaj.org.in>

24) WHO **(**World Health Organization), <http://www.whoindia.org/ **>**

25) BUKO Pharma-Kampagne, <http://www.epo.de/bukopharma/english.htm>
A campaign group committed to Rational Drug Therapy and involved in monitoring the German pharmaceutical industry. BUKO has about 200 member groups. Publication: *Pharma-Brief* in German.

26) ACT UP: AIDS Coalition to Unleash Power,
<http://www.actupny.org/>

27) Cochrane Collaboration Consumer, <http://www.cochrane.org/>

The Cochrane Collaboration Consumer Network summarises the findings of Cochrane systematic reviews of health research, helps people to understand research, and explains how people can participate in and contribute to it. Also see the Cochrane Reviews Index.

28) DES Centrum, The Netherlands, <http://www.descentrum.nl/>

Non-profit consumer organisation dedicated to informing the public about DES (diethylstilbestrol) and helping DES-exposed individuals. See also DES Action Canada at, <http://www.web.net/%7Edesact>

29) Database of Individual Patients' Experiences, DIPEx, <http://www.dipex.org/>, uses narrative video/audio interviews of people in the UK with high blood pressure, prostate cancer, breast cancer and colorectal cancer. In addition it provides reliable information about these conditions, and links to other sources; DIPEx is intended for patients, health professionals, researchers and policy makers and access is free.

30) IBFAN, <http://www.ibfan.org/>, the International Baby-Food Action Network - consists of public interest groups working around the world to reduce infant and young child morbidity and mortality. IBFAN aims to improve the health and well being of babies and young children, their mothers and their families through the protection, promotion and support of breastfeeding and optimal infant feeding practices.

31) International Society of Drug Bulletins**,** <http://www.isdbweb.org/>, (ISDB) is an organisation of therapeutic journals that are morally and financially independent of industry funding. ISDB members publish journals at least four times a year, aimed at health professionals and the public. Comparative information on drugs and treatments is a prominent topic

34) Social Audit, UK 's website, <http://www.socialaudit.org.uk/>, operated by Charles Medawar, the website is a mine of information, touching on a wide range of international drug policy issues, including DTCA, advertising control, marketing and promotional activity; conduct of clinical trials, secrecy in drug regulation and more.

36) The Hesperian Foundation, USA, <http://www.hesperian.org/>,
publishers of *Where there is no doctor*, *Helping Health Workers Learn,* and other such classics.

37) HealthWrights is a non-profit organization committed to advancing the health, basic rights, social equality, and self-determination of disadvantaged persons and groups. <http://www.healthwrights.org/aboutus.htm>, Many of current papers of David Werner are here.

38) The Politics of Health Knowledge Network "is a forum for the exploration of the impact of political decisions on health. We are concerned with how politics affect health on all levels – from individual organisms, to social groups, to the earth as a total ecological system.", <http://www.politicsofhealth.org/>

38) Public Citizen Health Research Group, USA at, <http://www.citizen.org/hrg/>
Site of *Worst Pills, Best Pills* book and more at, <http://www.worstpills.org/>

39) Consumer Project on Technology, <http://www.cptech.org/>, information and e-group archive IP Health for those interested in access to essential medicines and the politics of international trade, WTO, TRIPS, etc. See especially their page on IP Health: <http://www.cptech.org/ip/health/>

40) Médecins Sans Frontières (MSF) Access Campaign, <http://www.accessmed-msf.org/>

41) Consumers International (CI), <http://www.consumersinternational.org/>

42) International Network of Drug Information Centres INDICES, <http://www.prn.usm.my/sites/indices.html>, aims to advocate rational drug therapy throughout the world, particularly in developing countries, by providing global access to quality drug information.

43) International Network for the Rational Use of Drugs (INRUD), <www.inrud.org/>, was established in 1989 to design, test, and disseminate effective strategies to improve the way drugs are prescribed, dispensed, and used.

44) FSD-Alert, <http://www.fsd-alert.org/>, proposes a classification of women's sexual problems, one that gives appropriate priority to individual distress and inhibition arising within a broader framework of cultural and relational factors. Introduces an educational campaign that challenges the myths promoted by the pharmaceutical industry and calls for research on the many causes of women's sexual problems

---

45) Pharmweb, <www.pharmweb.net/>, since its launch in 1994 PharmWeb has developed into the premier online community of pharmacy, pharmaceutical and healthcare-related professionals with over 40,000 self-registered users. The first pharmaceutical portal on the Internet has developed into an invaluable directory of information, including a library of archives from over 100 moderated discussion forums. To browse the site either jump to a section using the pull-down menu or scroll down the home page to see what PharmWeb has to offer. PharmWeb is a registered trade mark.

46), The World Intellectual Property Organization (WIPO), <http://www.wipo.int/ipdl/en/>

47) The Tufts Center for the Study of Drug Development "is an independent, academic, non-profit research group affiliated with Tufts University.", <http://csdd.tufts.edu/>

Drug Information, Pharmacology, Pharmacy

48) USPDI, <http://www.uspdqi.org/>

49) Medline drug Information,
<http://www.nlm.nih.gov/medlineplus/druginformation.html>

50) Information on Drug - Where to Find, <http://www.nlm.nih.gov/services/drug.html>

51) The Internet Drug Index, <http://www.rxlist.com/>

52 Information on drugs and diseases at MayoClinic.com,
<http://www.mayoclinic.com/>

53) Clinical Pharmacology Online, <http://www.cponline.gsm.com/>

54) Drug Information Service, School of Pharmacy, University of Maryland,
<http://www.pharmacy.umaryland.edu/UMDI/>

55) E-drug Conference, Healthnet, INDIA-DRUG, <http://www.healthnet.org/>

56) The International Network for the Rational Use of Drugs, <http://www.inrud.org/>

57) Virtual Library of Pharmacy, <http://www.pharmacy.org/>

58) Therapeutic Guidelines, Australia, <http://www.tg.com.au/>

59) Pediatric Pharmacotherapy,
<http://www.people.virginia.edu/~smb4v/pedpharm/pedpharm.html>

60) Arizona Poison Page, <http://educ.ahsl.arizona.edu/poison.html>

61) National Poison Center of Malaysia by Professor Dzulkifli's team,
<http://www.prn.usm.my/>

62) Poison centers in the United States,
<http://singleparents.about.com/library/nblpoisonctrl.htm>

63) Medical & Clinical Toxicology Guide to the Internet,
<http://www.swmed.edu/toxicology/toxlinks.html>

64) RxList - The Internet Drug Index, <http://www.rxlist.com/>

65) Drug Information Service, the School of Pharmacy, University of Maryland, <http://www.pharmacy.umaryland.edu/UMDI/ >

66) Internet Mental Health medications, <http://www.mentalhealth.com/fr30.html>

67) Pharmacy Links, <http://www.geocities.com/HotSprings/1076/pharmacy.htm>

68) University of Sydney Pharmacy internet guide, <http://www.library.usyd.edu.au/subjects/pharmacy/links/>

69) The History of Pharmacy Museum, <http://www.pharmacy.arizona.edu/museum/page1.html>

70) Medline site, <http://www.nlm.nih.gov/medlineplus/>

71) Electronic Medicines, Compendium, <http://emc.vhn.net/>

72) Health Link site (formerly AHRTAG), <http://www.healthlink.org.uk/>

73) Pharmacotherapy, <http://pharmacotherapy.medscape.com/>

74) Pharma and The Oxford Pain Internet Site, <http://www.jr2.ox.ac.uk/bandolier/booth/painpag/ >

75) EPA (Environmental Protection Agency), <http://www.epa.gov/>

76) Swiss Toxicological Information Center, <http://www.toxi.ch/eng/>

77) Virtual Library-Pharmacy, <http://www.vh.org/navigation/vh/textbooks/>

78) The World-Wide Web Virtual Library: Epidemiology, <http://www.epibiostat.ucsf.edu/epidem/l>

79) The Center for Drug Evaluation and Research of the U.S. FDA, <http://www.fda.gov/cder>

80) Annual Review Pharmacology and Toxicology, <http://www.annurev.org/>

81) The Internet Drug Index, <http://www.rxlist.com/>

Drug Promotion

82) HealthySkepticism.org (formerly MaLAM: Medical Lobby for Appropriate Marketing), <http://www.healthyskepticism.org/>

83) No Free Lunch, < http://www.nofreelunch.org/>

84) Influence at Work (USA), <http://www.influenceatwork.com/>

85) Unbiased Medicine / Unbiased Psychiatry (USA), <http://www.unbiasedmedicine.org/>

86) The Center for Public Integrity, <http://www.publicintegrity.org>

87) PBS Frontline: Dangerous Prescription (USA), <http://www.pbs.org/wgbh/pages/frontline/shows/prescription/>

Access to Essential Drugs, WHO[1]

89) MDG Task Force Reports related to health and access to medicines, <http://www.unmillenniumproject.org/reports/reports2.htm>

90) * WHO Sites, <http://www.who.int/entity/en/>
* WHO EDM Useful Websites, <http://www.who.int/medicines/information/websites/infngo.shtml>

91) Model List of Essential Drugs, <http://www.who.int/medicines/areas/rational_use/en/index.html>

92) EDM Essential Medicines Library, <http://wwwsupply.unicef.dk/health/essentialdrugs.pdf >

93) EDM Information Resources, <http://www.who.int/medicines/information/infresources.shtml>

94) E-Drug (electronic discussion group on Essential Drugs in English), <http://www.essentialdrugs.org/>

96) Essential Drugs Monitor, <http://www.who.int/medicines/information/infmonitor.shtml/infmonitor.shtml>

---

[1] Please note urls ofWHO sited keep changing. So we give here only the topics in general.

97) Free Pharmaceutical Reference at, <http://www.drugref.org/ >

This is “a collaborative attempt at creating and maintaining an independent free pharmaceutical reference database. Our principles include: continuous peer review of all information; independence of industry; independence from funding related constraints independence from countries, health systems, and languages.”

98) Pharmaceuticals Programme of the WHO Regional Office for Europe, <http://www.euro.who.int/>

99) UNICEF Supply, <http://www.supply.unicef.dk/health/essentdrugs.htm>

100) WHO / Essential Drugs and Medicines Policy (EDM) Department, <http://www.who.int/medicines/>

101) WHO EDM documents list from A to Z, <http://www.who.int/medicines/library/docseng_from_a_to_z.shtml>

102) WHO EDM thematical list of documents, <http://www.who.int/medicines/library/theme/themelist.shtml>

103) WHO EDM-PAR-The New Emergency Health Kit, <http://www.who.int/medicines/library/par/new-emergency-health-kit/nehken.htm>

Formularies, Pharmacopoeia, Pharmacy, Pharmacology

104) WHO Formulary, <http://mednet3.who.int/mf/>

105) International Pharmacopoeia of WHO, <http://www.who.int/medicines/organization/qsm/activities/qualityassurance/pharmacopea/i-pharmacop.html>

106) WHO site on Norms and Standards: Quality, safety and efficacy of medicines, <http://www.who.int/medicines/areas/quality_safety/en/index.html>

107) British National Formulary, <http://www.bnf.org/>

108) The United States Pharmacopoeia (USPDI), <http://www.uspdqi.org/>

109) Martindale’s Extra Pharmacopoeia, <http://www.bradford.ac.uk/library/elecinfo/martindale.php>

110) Pharmacology Resources on the Web, <http://med-libwww.bu.edu/library/pharmres.html>

111) Merck Home Manual, <http://www.merck.com/pubs/mmanual_home/contents.htm>

112) Royal Pharmaceutical Society of Great Britain, <http://www.rpsgb.org.uk/ >

113) Virtual Pharmacy Libraries, <http://www.cpb.uoknsc.edu/pharmacy>

114) Pharmaceutical Info networks, <http://www.pharminfo.com/>

115) Glossary of Terms and Symbols Used in Pharmacology, <http://med-www.bu.edu/pharmacology/>

116) Pharmacology Resources, <http://www.aspet.org/public/pharm_resources/default.html>

117) Hardin MD (Univ of Iowa service) Pharmacology, <http://www.lib.uiowa.edu/hardin/md/pharmacology.html>

Health Information/Journals, ISDB International Society of Drug Bulletins

118) ISDB (International Society of Drug Bulletins) <http://66.71.191.169/isdbweb/pag/index.php>, The International Society of Drug Bulletins (ISDB) was founded in 1986. It aims to promote the international exchange of information of good quality on drugs and therapeutics, to encourage and to assist the development of professionally independent drug bulletins in all countries and facilitate cooperation among bulletins.

119) Bulletin of Drug & Health Information (BODHI) (email: <fha@cal.vsnl.net.in>)

120) Australian Prescriber, <http://www.australianprescriber.com/ >
121) Prescrire International (France, in English), <http://www.prescrire.org/>
122) British Medical Journal, <http://www.bmj.com/>
123) The Lancet, Lancet electronic research archive, <http://www.thelancet.com/search/advanced>

124) The Medical Journal of Australia, <http://www.mja.com.au/>
125) Annals of Internal Medicine, <http://www.annals.org/>
126) Archives of Internal Medicine, <http://archinte.ama-assn.org/>
127) CMAJ (Canadian Medical Association Journal), <http://www.cmaj.ca/>
128) Free Medline Search, <http://www.nlm.nih.gov/>

129) Electronic journals, <http://www.library.ucsf.edu/collres/journals/>

130) JAMA (Journal of the American Medical Association), <http://jama.ama-assn.org/>

131) MJA (Medical Journal of Australia), <http://www.mja.com.au/>

132) New England Journal of Medicine, <http://content.nejm.org/>

133) BMJ (British Medical Journal), <http://bmj.bmjjournals.com/index.dtl>

134) The Lancet, < http://www.thelancet.com/newlancet>

135) The Pharmaceutical Journal, <http://www.pharmj.com/>, is the official journal of the Royal Pharmaceutical Society of Great Britain.

136) Centre for Science in the Public Interest, <http://www.cspinet.org/>,
CSPI is a nutrition advacacy organisation. One of CSPI's major ways to educate the public is through our award-winning Nutrition Action Healthletter, the largest-circulation health newsletter in North America. CSPI also has an interest in integrity in science.

137) Evaluating the quality of Internet health information sources

138) Cambridge University Medical Library,
<http://www.medschl.cam.ac.uk/library/library.html>,
The Medical Library page, which enables users to find out about the Medical Library's collections, services and facilities; to check the details and location of books, journal titles and articles whether they are held in Cambridge or elsewhere; to keep up-to-date with the biomedical literature by searching bibliographic databases; to access electronic publications such as reference books and on-line journals.

139) Centre for Health Promotion University of Toronto,
<http://www.utoronto.ca/chp/>,
Its mission is to conduct research and educational activities as well as to provide service in the field of health promotion, defined as "the process of enabling people to increase control over, and to improve their health".

140) Health*Insite*, <http://www.healthinsite.gov.au/>,
Health*Insite* is a World Wide Web server which was constructed to provide the first point of entry for those seeking quality information about Australian health & related products and services.

141) INASP International Network for the Availability of Scientific Publications is a co-operative network of partners aiming to improve world-wide access to scientific information.

142) Medical Matrix, <http://www.medmatrix.org/reg/login.asp>,
The Medical Matrix Project is devoted to posting, annotating, and continuously updating "full content, unrestricted access, Internet clinical medicine resources." Our target audience is primarily United States physicians and healthworkers who are on the front line in prescribing treatment for disease conditions.

143) US National Library of Medicine, <http://www.nlm.nih.gov/>

Rational Use of Drugs

144) WHO Guide to Good Prescribing,
<http://www.med.rug.nl/pharma/who-cc/ggp/homepage.htm>

145) International Network for the Rational Use of Drugs (INRUD),
<http://www.msh.org//inrud/>

Medicines Pricing Policy in India and Other Countries

146) National Pharmaceutical Pricing Authority (NPPA), India,
<http://www.nppaindia.nic.in/>

147) Medicine Policy in Netherlands,
<http://www.netherlands-mbassy.org/article.asp?articleref=AR00000251EN>

148) Pharmaceutical Benefits Pricing Authority (Australia),
<http://www.health.gov.au/pbs/general/pricing/pbparpt.htm>

150) Patent Medicine review Board sets the medicine prices in Canada,
<http://www.pmprb-cepmb.gc.ca/english/home.asp?x=1>

151) European Commission website has information about pricing policies of a number of countries including France, Germany, Sweden, United Kingdom. At the following website, <http://pharmacos.eudra.org/>

152) The Netherlands Pharmaceutical Pricing and Reimbursement Policies,
<http://pharmacos.eudra.org/F3/g10/docs/tse/Netherlands.pdf>

153) Australia, <http://pharmacos.eudra.org/F3/g10/docs/tse/Australia.pdf>

155) New Zealand Pharmaceutical Pricing and Reimbursement Policies,
<http://pharmacos.eudra.org/F3/g10/docs/tse/NewZealand.pdf>

156) Finland Pharmaceutical Pricing and Reimbursement Policies,
<http://pharmacos.eudra.org/F3/g10/docs/tse/Finland.pdf>
Sweden, <http://pharmacos.eudra.org/F3/g10/docs/tse/Sweden.pdf>

157) WHO website on drug prices,
<http://www.who.int/medicines/organization/par/ipc/drugpriceinfo.shtml>

158) International Drug Price Indicator Guide,
<http://erc.msh.org/mainpage.cfm?file=1.cfm&id=1&temptitle=Introduction&module=DMP&language=English>

Pharma Business

159) Pharma business in India, <http://www.pharmabiz.com>

160) Also, <http://www.expresspharmapulse.com/>

161) Scrip Magazine, <http://www.pjbpubs.com/scrip_magazine/>

162) International Organization on Generic Drugs, <http://www.egagenerics.com/>

163) Pharmaceutical Research and Manufacturers of America <http://www.phrma.org/ >

164) The International Federation of Pharmaceutical Manufacturers Association, <http://www.ifpma.org/>

165) Indian Drug Manufacturers' Association, <http://www.idma-assn.org/>

166) Organisation of Pharmaceutical Producers of India, <http://www.indiaoppi.com/>

167) Business Information on India's drug industry,
<http://www.indiainfoline.com/phar/>
And, <http://www.myiris.com>

US FDA and EU related

168) US FDA, <http://www.fda.gov>
169) US FDA Orange Book, <http://www.fda.gov/cder/ob/default.htm>
170) US FDA CDER, <http://www.fda.gov/cder/>
171) Network Services for the European Union Pharmaceutical Regulatory Sector, <http://www.eudra.org/>

189) European Medicines Evaluation Agency, <http://www.emea.eu.int/>,
A new European system for the authorisation of medicinal products since January 1995 Designed to promote both public health and the free circulation of pharmaceuticals. Access to the European market is facilitated for new and better medicines, benefiting both patients and the European pharmaceutical research. The new European system is based on co-operation between the national competent authorities of the Member States and the London-based European Agency for the Evaluation of Medicinal Products (EMEA).
The EMEA acts as the focal point of the new system, co-ordinating the scientific resources made available by national authorities, including a network of 2,000 European experts.
190) UK Current Problems in Pharmacovigilance

191) UK The Path of Least Resistance. Standing Medical Advisory Committee, Sub-Group on Antimicrobial Resistance,
<http://www.advisorybodies.doh.gov.uk/smac1.htm>
192) US FDA AERS (Adverse Event Reporting System- formerly ADR) Data Files,
<http://www.fda.gov/cder/aers/default.htm>
193) US FDA and the Internet: advertising and promotion of medicinal products,
<http://www.fda.gov/opacom/morechoices/transcript1096/fdainet.html>
194) <http://www.fda.gov/cder/warn/index.htm>
195) <http://www.nih.gov>

TRIPS/WTO/IPR

172) FAQs about TRIPS, <http://www.wto.org/english/tratop_e/trips_e/tripfq_e.htm>

173) WTO website, <www.wto.org>

174) WTO watch and related sites,

<http://www.iatp.org/>

175) Access to Essential Medicines/CPT,
<http://www.cptech.org/ip/health/>

176) Report of Commission on Intellectual Property Rights,
<http://www.iprcommission.org>

177) On Patents, <http://www.patent.freeserve.co.uk/>

178) Responsible Genetics,
<http://www.gene-watch.org/>

179) Third World Network,
<http://www.twnside.org.sg/twr.htm>

Life Sciences and Health Sciences

180) On the Human Genome Project, <http://homepage.smc.edu/hgp/>

181) The Virtual Nursing Center

A large collection of nursing resources.

182) Morbidity and Mortality Weekly Report, <http://www.cdc.gov/mmwr/>

183) Based on CDC weekly reports, site also provides public health articles of interest

184) General Internet Health Resources

Provides a good explanation of the recommended sites, and has links to these sites.

185) MedWeb, <http://www.medweb.emory.edu/MedWeb/>

Another seach database for medical sites. Search by keyword, or perform an advanced search for more specific results.

186) National Library of Medicine, <http://www.nlm.nih.gov/>

Information about the National Library of Medicine, electronic resources, searchable catalog (Medline), publications, and medical news.

187) The Visible Human Project, <http://www.nlm.nih.gov/research/visible/>

Sample MRI and CAT scan images

188) Medical Physiology, <http://mphywww.tamu.edu/>

Texas A&M University Health Science Center's Department of Medical Physiology.

Evidence Based Medicine

188) Bandolier, <http://www.jr2.ox.ac.uk/Bandolier/>, is produced monthly in Oxford for the UK NHS R&D Directorate. It contains bullet points (hence Bandolier) of evidence-based medicine.

196) Clinical Evidence, <http://www.clinicalevidence.com/ceweb/conditions/index.jsp>, a compendium of the best available research findings on common and important clinical questions, updated and expanded every six months.

Cochrane Collaboration (Australasian), <http://www.cochrane.org.au/>, (this site provides links to the many other Cochrane sites.)

197) The Cochrane Collaboration, <http://www.cochrane.org/index0.htm>, is an international organisation that aims to help people make well-informed decisions about

healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of healthcare interventions.

198) Evidence Based Health Informatics at Health Information Research Unit, <http://hiru.mcmaster.ca/>

Evidence based health care promotes the collection, interpretation, and integration of valid, important and applicable patient-reported, clinician-observed, and research-derived evidence. The best available evidence, moderated by patient circumstances and preferences, is applied to improve the quality of clinical judgements and facilitate cost-effective health care.

199) Informed Health Online, <http://www.informedhealthonline.org/>, Updated health information you can trust from the Health Research and Education Foundation Ltd. The Foundation is a not-for-profit health promotion organisation based in Melbourne, Australia.

200) NHS Centre for Reviews and Dissemination, <http://www.york.ac.uk/inst/crd/>

201) New Zealand Guidelines Group, <http://www.nzgg.org.nz/>, The NZGG is an independent, not-for-profit organisation set up to promote effective delivery of health and disability services, based on evidence.

Guidelines

202) Canadian Medical Association, <http://www.cma.ca/cpgs/index.htm>, The clinical practice guidelines in this collection were produced or endorsed in Canada by a national, provincial or territorial medical or health organization, professional society, government agency or expert panel.

203) <http://www.ahrq.gov/> , contains a master listing of the information products of the Agency and how to obtain them, and is part of the Government Information Locator Service (GILS)

204) Textbooks

High quality textbooks should be comprehensive, be frequently updated, have explicit links to evidence, and be organized for easy and effective searching. A good example of an electronic textbook is Scientific American Medicine Online, an online version of the comprehensive medical textbook. It has an excellent reputation and a commitment to updates.

205) EMBASE

EMBASE is the Excerpta Medica database for biomedical and pharmaceutical journal articles. This database indexes 3,500 journals, a somewhat different spectrum compared with Medline, with more international (including Canadian) journals and fewer state, nursing, veterinary medicine, or dentistry journals than Medline. EMBASE is available from 1988 on and is searchable by a controlled vocabulary, also with subheadings; the structure and organization of EMBASE is especially useful for searching for evidence regarding drugs and pharmaceuticals. As with Medline, the individual articles cited must be scrutinized for their validity and quality.

206) Drug, device, diagnostics approvals & clinical trials glossary,
<http://www.genomicglossaries.com/content/drug_approvals.asp>

Recent Books and Reports

1) *The $800 Million Pill: The Truth behind the Cost of New Drugs.* Merrill Goozner University of California Press., Berkley, California, USA., 2004, 297 pp. $24.95.

2) *The Truth About the Drug Companies: How they deceive us and what to do about it.* Marcia Angell. 305 pp. Random House, 2004. $ 24.95.

3) *On the Take: How America's Complicity with Big Business Can Endanger Your Health*, Jerome P. Kassirer, Oxford University Press, October 2004.

4) *The Influence of the Pharmaceutical Industry,*
<www.publications.parliament.uk/ pa/cm200405/cmselect/cmhealth/42/42.pdf>2004a.

5) *The World Medicines Situation.* WHO, Geneva, 2004.
<www.who.int/medicines/organization/par/World_Medicines_Situation.pdf>.

For Building a Library on Medicines

The references and links given above and those cited throughout this book would be helpful as well as the following. The following is a minimum desirable list. Some of these will be repetitive.

Medical Journals

Annals of Internal Medicine
British Medical Journal
Journal of the American Medical Association
Lancet
New England Journal of Medicine

Drug and Toxicology Information and Pharmacology Journals
British Journal of Clinical Pharmacology
Clinical Pharmacology and Therapeutics
European Journal of Clinical Pharmacology
Human and Experimental Toxicology
Journal of Toxicology and Clinical Toxicology
Medical Toxicology and Adverse Drug Experience
Australian Prescriber
Prescrire (France)

Pharmacy Journals

American Journal of Hospital Pharmacy
Annals of Pharmacotherapy
Clinical Pharmacy
DICP-Annals of Pharmacotherapy
Journal of Clinical and Hospital Pharmacy
Journal of Clinical Pharmacy and Therapeutics
Pharmaceutical Journal UK
Eastern Pharmacist
Indian Drugs

Journals in Specific Areas

American Journal of Emergency Medicine
Annals of Emergency Medicine
British Journal of Obstetrics and Gynaecology
Critical Care Medicine
Journal of Antimicrobials and Chemotherapy
Journal of Infectious Diseases
Journal of Paediatrics and Child Health

Essential Journals in Specific Areas
American Journal of Emergency Medicine
Annals of Emergency Medicine
British Drugs Lists and Therapeutic Formularies
British National Formulary, updated every six months

Essential Drug Lists

Essential Medicines List, Ministry of Health, Govt. of India (2003)

The WHO Model Lists of Essential Drugs 14th edition (March 2005)

See also: "Medicines Policy and Standards, Technical Cooperation for Essential Drugs and Traditional Medicine" at, <http://www.who.int/medicines/en/>

Some Useful addresses in India

Drug Controller of India,
Nirman Bhavan, New Delhi 110 011

Drug Technical Advisory Board (DTAB), c/o, Drug Controller of India
Nirman Bhavan, New Delhi 110 011

Editor, BODHI (Bulletin of Drug Health and Information), 254 Lake Town, Calcutta 700 089

All-India Drug Action Network (AIDAN), email: <aidanindia@yahoo.com>

Basic References for a Drug Information Library

Latest editions of:

American Medical Association (AMA) drug evaluations

American Hospital Formulary Service (AHFS) drug information

British National Formulary

Drug availability reference (specific for the country or region)

Ellenhorn and Barceloux, Medical toxicology: Diagnosis and Treatment of Human Poisoning, or another clinical toxicology or poisoning text

Goodman and Gilman, The Pharmacological Basis of Therapeutics, or another basic pharmacology text like Lawrence and Bennett, Clinical Pharmacology, or Rang and Dale, Pharmacology (see below *Other reference books on drugs*)

Gosselin, Smith, and Hodge, Clinical Toxicology of Commercial Products

Hathi Committee Report (1975)

Justice Lentin Commission's Report (1986)

National Formulary of India or essential drugs list of Govt. of India

Pediatric Drugs Formulary, Meherban Singh and AK Deorari of Indian Academy of Pediatrics

Price reference (specific for the country or region) as in MIMS, CIMS or Pamposh Pharmaceutical Guide (Publishers of Eastern Pharmacist, New Delhi)

Textbook of Internal medicine (such as Harrison's Principles of Internal Medicine or the Oxford Textbook of Medicine)

Tropical Medicine Reference including reference books on malaria, TB, leprosy, ARI, diarrhoeal diseases

United States Pharmacopeia-Drug Information (USP-DI) for health professionals and patients

WHO Basic Information Resources

WHO Pharmaceutical Newsletter
WHO Drug Information
Essential Drugs Monitor
WHO Model Prescribing Information
WHO Technical Report Series
The Use of Essential Drugs (TRS 867). Model List of
Essential Drugs, 1997
WHO Model Prescribing Information: Drugs Used in Anesthesia, Parasitic Disease, Mycobacterial Diseases, Sexually Transmitted Diseases, Skin Diseases

References Books on Drugs (look for latest editions)

1. Martindale, The Extra Pharmacopoeia

2. The Pharmacological Basis of Therapeutics: Goodman L.S. & Gilman A

3. Physicians' Desk Reference

4. Consolidated List of Products whose consumption and/or sale has been banned withdrawn, severely restricted or not approved by governments. : UNITED NATIONS

5. Iatrogenic Diseases: P.F.D'Arcy and J.P.Griffin, Oxford University Press

6. British National Formulary

7. USPDI : US Pharmacopeial Convention Inc

8. Textbook of Adverse Drug Reactions : Second Ed. 1981

Davies D.M. Oxford University Press

9. Textbook of Pharmacology: Laurence and Bennett, Churchill Livingstone

10. Pharmacology and Pharmacotherapeutics: Satoskar and Satoskar, Popular Press, Bombay

11. Drugs for Children: WHO, Geneva,

12. Drugs for the Elderly: WHO, Geneva

13. Guide to Good Prescribing: WHO, Geneva

14. Estimating Drug Requirements: WHO, Geneva

15. (Treatment) Guidelines on Analgesics, Antibiotics, Psychotropics, Cardiovascular and Respiratory Drugs: Victorian Medical Postgraduate Foundation Inc., 'Chelsea House', 3rd Floor, 55 Flemington Road, North Melbourne, VI C, 3051, Australia.

16. How to Investigate Drug Use in Health Facilities: WHO, Geneva

18. Managing Drug Supply. Management Sciences for Health:

Some Sources of People-oriented Drug Information and Related Issues

Periodicals

1. Medico Friend Circle Bulletin, <www.mfcindia.org>

2. Health Action: Catholic Hospital Association of India, 15/6, Staff Road, P.Box 2126, Secunderabad-500 003 (AP)

3. Essential Drugs Monitor: WHO

4. Central Council for Research in Unani Newsletter : 5 Panchsheel Shopping Center, New Delhi 110 017

5. Australian Prescriber, < www.australianprescriber.com>

6. MALAM (Medical Lobby for Appropriate Marketing), <http://www.mja.com.au/public/issues/xmas/mansfield/mansfield.html >

7. BODHI (Bulletin of Drug Health and Information): 254 Lake Town, Calcutta 700 089

8. Prescrire Intl: PO Box 459, F-75527, Paris Cedex 11, France

9. Issues in Medical Ethics: Forum for Medical Ethics Society, 310 Prabhu Darshan, S.Sainik, Nagar, Amboli, Andheri (W), Mumbai 400 058

Pharma related Business and Trade Journals from India

1. Pharmabiz at, <http://www.pharmabiz.com/>
2. Express Pharma Pulse: Indian Express, Nariman Point, Mumbai - 400 021, <http://www.expresspharmapulse.com/>

3. Monthly index of Medical Specialities (MIMS): 90, Nehru Place, New Delhi - 110 019

4. Current Index of Medical Specialities (CIMS): Biogard Medical Services, 640, 10-A Cross, West of Chord Road (II Stage), Bangalore - 560 086

5. IDMA Bulletin: Indian Drug Manufacturers', 102-B, Poonam Chambers, Dr. A.B. Road, Worli, Mumbai - 400 018

6. Drug Today: 1, Mother Dairy, Commercial Complex, Mayur Vihar, Pocket-1, Phase 1, New Delhi - 110 001

7. Indian Pharmaceutical Guide: Pamposh Publications, 506, Ashok Bhavan, 91, Nehru Place, New Delhi - 110 019